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Abstract

Functional strength training versus movement performance therapy for upper limb motor recovery early after stroke: a RCT

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Background: Not all stroke survivors respond to the same form of physical therapy in the same way early after stroke. The response is variable and a detailed understanding of the interaction between specific physical therapies and neural structure and function is needed.

Objectives: To determine if upper limb recovery is enhanced more by functional strength training (FST) than by movement performance therapy (MPT), to identify the differences in the neural correlates of response to (1) FST and (2) MPT and to determine whether or not pretreatment neural characteristics can predict recovery in response to (1) FST and (2) MPT.

Design: Randomised, controlled, observer-blind, multicentre trial with embedded explanatory investigations. An independent facility used computer-generated randomisation for participants' group allocation.

Setting: In-patient rehabilitation, participants' homes, university movement analysis facilities and NHS or university neuroimaging departments in the UK.

Participants: People who were between 2 and 60 days after stroke in the territory of the anterior cerebral circulation, with some voluntary muscle contraction in the more affected upper limb but not full function.

Interventions: Routine rehabilitation [conventional physical therapy (CPT)] plus either MPT or FST in equal doses during a 6-week intervention phase. FST was progressive resistive exercise provided during training of functional tasks. MPT was therapist 'hands-on' sensory input and guidance for production of smooth and accurate movement.

Main outcomes: Action Research Arm Test (ARAT) score for clinical efficacy. Neural measures were made of corticocortical [fractional anisotropy (FA) from corpus callosum midline], corticospinal connectivity (asymmetry of corticospinal tracts FA) and resting motor threshold of paretic biceps brachii (pBB) and extensor carpi radialis muscles (derived from transcranial magnetic stimulation).

Analysis: Change in ARAT scores were analysed using analysis of covariance models adjusted for baseline variables and randomisation strata. Correlation coefficients were calculated between change in neural measures and change in ARAT score per group and for the whole sample. An interaction term was calculated for each baseline neural measure and ARAT score change from baseline to outcome.

Results: A total of 288 participants were randomised [mean age 72.2 (standard deviation 12.5) years; mean ARAT score of 25.5 (18.2); $n = 283$]. For the 240 participants with ARAT measurements at baseline and outcome, the mean change scores were FST + CPT = 9.70 (11.72) and MPT + CPT = 7.90 (9.18). The group difference did not reach statistical significance (least squares mean difference 1.35, 95% confidence interval -1.20 to 3.90; $p = 0.298$). Correlations between ARAT change scores and baseline neural values ranged from -0.147 ($p = 0.385$) for whole-sample corticospinal connectivity ($n = 37$) to 0.199 ($p = 0.320$) for MPT + CPT resting motor threshold pBB ($n = 27$). No statistically significant interaction effects were found between baseline neural variables and change in ARAT score. There were no differences between groups in adverse events.

Limitations: The number of participants in the embedded explanatory investigation was lower than expected.

Conclusions: The small difference in upper limb improvement in response to FST and MPT did not reach statistical significance. Baseline neural measures neither correlated with upper limb recovery nor predicted therapy response.

Future work: Needs to continue investigation of the variability of response to specific physical therapies in people early after stroke.

Trial registration: Current Controlled Trials ISRCTN19090862 and National Research Ethics Service reference number 11/EE/0524.

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List of abbreviations

9HPT	Nine-Hole Peg Test	MNI	Montreal Neurological Institute
AE	adverse event	MPT	movement performance therapy
ANCOVA	analysis of covariance	MR	magnetic resonance
ARAT	Action Research Arm Test	MRC	Medical Research Council
CI	confidence interval	MRI	magnetic resonance imaging
CIMT	constraint-induced movement therapy	pBB	paretic biceps brachii
CLRN	Comprehensive Local Research Network	pECR	paretic extensor carpi radialis
CONSORT	Consolidated Standards of Reporting Trials	PPI	Patient and Public Involvement
CPT	conventional physical therapy	PPIRes	Patient and Public Involvement in Research
CRF	case report form	RAT	robot-assisted therapy
CST	corticospinal tract	RCB	Robertson Centre for Biostatistics
DMEC	Data Monitoring and Ethics Committee	RCT	randomised controlled trial
EME	Efficacy and Mechanism Evaluation	RMT	resting motor threshold
FA	fractional anisotropy	SAE	serious adverse event
FSL	FMRIB's Software Library	SAP	statistical analysis plan
FST	functional strength training	SD	standard deviation
GCP	good clinical practice	SOP	standard operating procedure
ICC	intraclass correlation coefficient	TMS	transcranial magnetic stimulation
MEP	motor-evoked potential	TSC	Trial Steering Committee
		UEA	University of East Anglia
		WMFT	Wolf Motor Function Test

Plain English summary

Recovery of the arm and hand (upper limb) after stroke is a research priority. We need to know which people should receive which type of physical therapy and how different types of physical therapy drive brain recovery after stroke.

The two physical therapies investigated were functional strength training (FST) and movement performance therapy (MPT). FST is strength training during everyday tasks, for example picking up a cup that contains more water as the person improves. MPT is provided by a therapist using 'hands-on' techniques to aid moving more smoothly and accurately.

Random allocation was used so that each participant had a 50% chance of receiving FST or MPT. All participants undertook measures of ability to move their upper limb before treatment, after the 6-week treatment phase and at 6 months after stroke. In participants with no history of epilepsy/seizures and no metal in their bodies (e.g. pacemaker) we undertook measures of (1) the brain damage caused by stroke and (2) the strength of the connection between brain and weak muscle. These neural measures were carried out before and after the treatment phase.

We found no difference between FST and MPT because some people in each group responded better than others.

The before-treatment neural measures did not predict improvement. The neural changes from before to after treatment were similar in the two groups.

These findings confirm suggestions from earlier trials that people respond differently to different physical therapies. Future work should investigate why some people respond better to FST and MPT than others.

Scientific summary

Background

The trial reported here focused on the top 10 research priorities identified by people who have had a stroke, namely upper limb recovery after stroke. This is because of the need for upper limb dexterity to perform everyday tasks, such as drinking from a cup, unscrewing the top from a bottle of water and fastening buttons/zips, for independent living. Evidenced-based physical therapy does enhance upper limb recovery, but at 6 months after stroke only 38% of people have some dexterity. Therefore, there is a need for even better methods of upper limb rehabilitation.

It is known that (1) upper limb recovery is enhanced by physical therapy based on repetitive practice of everyday tasks and (2) the 3 months immediately after stroke is when recovery is most rapid and there is most potential for brain recovery. But not everybody responds in the same way to particular forms of task-specific training. A key influence on therapy response may be the interindividual differences in how the stroke affects the brain and, therefore, the neurobiological potential for recovery. Indeed, there is a variety of neural deficits after stroke seen in different combinations in different people. Therefore, it is important to have a greater understanding of how these neural deficits influence how people respond to specific physical therapies.

The trial reported here focused on how different neural deficits early after stroke (1) could predict how an individual may respond to different physical therapies (neural predictive markers) and (2) may change in response to those therapies (underlying neural mechanisms). Gaining this greater understanding will progress clinical practice in two ways. First, knowing the neural mechanisms of upper limb recovery will enable targeting of physical therapy at what needs to change. Second, knowing the neural predictors of response to specific physical therapies will enhance accuracy of evidenced-based decisions as to what is the most appropriate therapy for individuals after stroke. These decisions are currently based only on watching how people move (www.viatherapy.org; accessed 10 May 2018).

The specific forms of physical therapy employed in the trial reported here were functional strength training (FST) and movement performance therapy (MPT). FST is focused on improving ability to perform everyday functional tasks. MPT is focused on enhancing quality of movement required for everyday functional tasks. Such conceptually different physical therapies have been found to be no more or less effective than each other. However, our earlier trials found variation between people in response to MPT and FST. Therefore, a comparison of FST and MPT was the context for investigating the neural predictors of response to and mechanisms of action of specific physical therapies.

Objectives

1. To determine if upper limb motor recovery is enhanced more by FST + conventional physical therapy (CPT) than by an equal dose of MPT + CPT commenced early after stroke.
2. To identify the similarities and differences in the neural correlates of clinical (observed movement) improvement in upper limb motor function in response to (1) FST + CPT and (2) MPT + CPT.
3. To determine whether any pretreatment neural characteristics or combination of (1) anatomical location of infarction, (2) volume of the stroke lesion, (3) residual structural corticocortical connectivity, (4) residual corticospinal connectivity and (5) brain–muscle functional connectivity [derived from transcranial magnetic stimulation (TMS)] are sufficiently predictive of upper limb recovery after stroke to enable physical therapy to be targeted at those people most likely to respond.

Methods

Design

A randomised, controlled, observer-blind, two-group, multicentre trial with embedded neural measures. The primary end point was at outcome, which was after the end of the 6-week intervention phase. The secondary end point was at 6 months after stroke.

Setting and participants

Participants were recruited from three stroke services (Birmingham, Staffordshire and Norfolk) and were followed up until 6 months after stroke, wherever they were residing. Study criteria (combined inclusion and exclusion) were people:

- who were between 2 and 60 days after stroke in the territory of the anterior cerebral circulation when providing informed consent
- aged ≥ 18 years
- who were able, before the index stroke, to use the paretic, contralesional, upper limb to lift and then drink from a cup
- who were defined as 'medically stable', as confirmed by the stroke service medical team
- with enough voluntary muscle contraction in the paretic upper limb to begin to move (score of at least 11 of the 33 points of the Motricity Index pinch section) but unable to complete the Nine-Hole Peg Test (9HPT) within 50 seconds
- with no obvious spatial neglect (scored 0 or 1 on the Extinction and Inattention subscale of the National Institutes of Health Stroke Scale)
- who could imitate action with the non-paretic (ipsilesional) upper limb.

Randomisation

Group allocation order was generated before the trial began and was stratified by clinical centre, time after stroke (up to 30 days and 31–60 days) and ability to use the paretic upper limb as assessed by the 9HPT (substantial = move one peg or fewer in 50 seconds and moderate = move 2–8 pegs in 50 seconds). An independent telephone randomisation service concealed treatment allocation from investigators, research therapists and blinded assessors prior to randomisation of a participant.

Interventions

All participants were provided with routine conventional physical therapy (CPT), as deemed appropriate by the clinical therapists and then either extra MPT or FST in the same dose (amount in minutes).

MPT was prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week for up to 6 weeks (CPT + MPT group). Training in delivering MPT was provided.

FST was prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week (FST + CPT group). Training in delivering FST was provided.

Outcome measures

Clinical efficacy measures were made before randomisation (baseline), the working day (± 7 days) after the 6-week intervention ends (outcome) and 6 calendar months (± 14 days) after the index stroke. The primary outcome measure was the Action Research Arm Test (ARAT) score. Secondary outcome measures were the Wolf Motor Function Test (WMFT), and the Hand Grip Force and Pinch Grip Force tests.

Neural measures were made within 10 days after the clinical efficacy measures at baseline and at outcome. These were (1) anatomical location of infarction, (2) volume of the stroke lesion, (3) residual structural corticocortical connectivity, (4) residual corticospinal connectivity and (5) brain–muscle functional connectivity (derived from TMS).

Sample size and power

The sample size calculation considered clustered data structure (patients within therapist within treatment group) and actual ARAT score data from our earlier trial. Assuming an intraclass correlation coefficient (ICC) of 0.01 in both treatment arms and three centres with a separate therapist for each randomised arm, a sample size of 99 participants per group had 80% power to detect a clinically important mean difference of 6.2 in ARAT score change when analysing data using a two-sample *t*-test with Satterthwaite correction. This applied a 5% two-sided significance level and allowing for potentially different standard deviations (SDs) in the CPT + MPT (SD 7.9) and CPT + FST (SD 9.3) groups. To account for clustering in the design a sample size inflation factor $1 + (m - 1) \times \text{ICC}$ was applied (m = cluster size). To allow for an attrition rate of 10% (7% in our previous single-centre trial), 288 participants were recruited (144 per group).

Statistical analyses

In accordance with the intention-to-treat principle, all participants were analysed according to the group to which they were randomly allocated. The statistical analysis plan was agreed, signed and dated prior to the database lock and unblinding of the treatment allocations. There was a change to the original analysis plan from taking account of clustering by therapist to only adjusting for study site, as it was not always practical for participants to have the same therapist for all their sessions.

Clinical efficacy (objective 1)

The analysis compared the change in the efficacy parameters (baseline and outcome) between the treatment groups using analysis of covariance (ANCOVA) models adjusted for the baseline value and randomisation strata (time after stroke, ability to use paretic upper limb, clinical centre). Adjusted least squares mean difference and 95% confidence intervals are reported. When the outcome distribution deviated from a normal distribution, a log or other appropriate transformation was applied.

Neural correlates of clinical improvement (objective 2)

Associations between the changes in neural variables were compared with the changes in clinical efficacy measures (baseline to outcome). Correlation coefficients were calculated for the two treatment groups separately and for the groups combined.

Predictive neural markers of clinical improvement (objective 3)

For each baseline covariate being investigated as a potential predictive marker of clinical improvement, the treatment effect (change in ARAT score) was calculated within each level of the subgroup (adjusted as for the first objective) and an interaction term between randomised treatment and baseline covariate was included in the model.

Adverse events

All adverse events (AEs) were recorded from date of randomisation to end of trial. To report serious adverse events (SAEs) the trial team used the Norwich University Hospital NHS Trust and University of East Anglia joint standard operating procedure (SOP). The latest version can be found at www.nnuh.nhs.uk/publication/sop-205-adverse-events/ (accessed 11 May 2018). All SAEs were followed up until a documented end date and resolution could be provided, or the participant ended the trial.

Results

A total of 5064 stroke survivors were screened for eligibility. Of these stroke survivors, 2929 were excluded as they did not meet the initial study inclusion criteria. Of the remaining potential participants, 536 declined participation and, consequently, 481 provided informed consent. Of these, 138 did not meet the eligibility criteria and a further 55 withdrew informed consent. Therefore, 288 participants were randomised. Informed consent was provided within 30 days of stroke by 59% of participants and at ≥ 31 days by 41%. Baseline characteristics were balanced across groups.

Clinical efficacy (objective 1)

The mean age of participants was 72.2 (SD 12.5) years ($n = 288$) and the mean ARAT score was 25.5 (SD 18.2) ($n = 283$).

For the 240 participants with a total ARAT score at baseline and outcome, the mean change scores were 9.70 (SD 11.72) for FST + CPT and 7.90 (SD 9.18) for MPT + CPT. The group difference did not reach statistical significance ($p = 0.298$).

For the 204 participants with a total ARAT score at baseline and follow-up, the mean change scores were FST + CPT = 11.10 (SD 14.68) and MPT + CPT = 10.30 (SD 10.74). The group difference did not reach statistical significance ($p = 0.743$).

For secondary outcomes, WMFT and Hand Grip Force and Pinch Grip Force tests, there were small differences between the groups in change from baseline at outcome and follow-up. But these differences did not reach statistical significance.

Neural correlates of clinical improvement (objective 2)

Analysis was undertaken per neural variable for those people with that variable and a total ARAT score at both baseline and outcome. Consequently, the number of participants varied across aspects of the analysis. Correlations between change in total ARAT change scores and baseline neural values ranged from -0.147 ($p = 0.385$) for whole-sample corticospinal connectivity ($n = 37$) to 0.199 ($p = 0.320$) for MPT + CPT resting motor threshold paretic biceps brachii ($n = 27$).

Predictive neural markers of clinical improvement (objective 3)

Analysis was undertaken per neural variable for those people with that variable at baseline and a total ARAT score at both baseline and outcome.

No statistically significant interaction effects were found between baseline neural variables and change in ARAT score.

Adverse events

There were no differences between groups in the number of AEs.

Conclusions

Clinical efficacy (objective 1)

The trial found small differences in the clinical efficacy of upper limb recovery between FST + CPT and MPT + CPT, but these did not reach statistical significance. Both groups showed increase in ARAT score (primary outcome measure) above the clinically important change, but variation around the mean change from baseline scores was substantial in both groups.

Neural correlates of clinical improvement (objective 2)

The neural correlates of change were similar for the two forms of physical therapy.

Objective 3

The trial reported here found that none of the pretreatment neural characteristics of interest predicted response to either FST + CPT or MPT + CPT.

Implications for health care

The findings of the trial reported here confirm clinical impressions and emerging research evidence of variation in response to specific therapies among people early after stroke.

Research recommendations

There is still an urgent need for evidence to guide decisions about (1) appropriate prescription of physical therapy for individuals and (2) the recovery mechanisms at which physical therapy should be targeted.

Trial registration

This trial is registered as ISRCTN 19090862 and National Research Ethics Service reference number 11/EE/0524.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership.

Chapter 1 Introduction

The trial reported here focused on a top 10 research priority identified by people who have had a stroke, namely upper limb recovery after stroke.¹ Upper limb recovery is a research priority because of the need to perform everyday tasks such as drinking from a cup, unscrewing the top from a bottle of water and fastening buttons/zips for independent living. Difficulty with these and other everyday tasks is a frequent consequence of stroke. Indeed, upper limb neuromuscular weakness (paresis) has been estimated as occurring in 77% of people after stroke.² Upper limb recovery is therefore a key target for rehabilitation, but at 6 months after stroke, only 38% of people have some dexterity.² 'Better methods of upper limb rehabilitation' are required.¹

The socioeconomic impact of residual upper limb disability is high. Indeed, stroke alone produces most of the adult disability across the globe.³ In England alone, each year around 110,000 people have a stroke and the estimated annual cost is £9B.⁴ Most of the cost is in 'rehabilitation and life after stroke' (reproduced with permission from the National Audit Office⁴). The impact is unlikely to lessen because most people who have a stroke are > 65 years, and the population is ageing. Improving the outcome of upper limb rehabilitation after stroke is a research priority for the NHS⁵ and, more widely, across Europe.⁶

It is known that (1) upper limb recovery is enhanced by the provision of physical therapy based on repetitive task-specific training,⁷ and (2) the 3 months immediately after stroke is when recovery is most rapid⁸ and there is most potential for central nervous system reorganisation (neuroplasticity).⁹ However, not everybody responds in the same way to particular forms of task-specific training. For example, constraint-induced movement therapy (CIMT) is suitable only for people with at least 10° of voluntary movement of the paretic thumb and two or more fingers^{10,11} who are between 3 and 9 months after stroke.¹² When used with people early after stroke, CIMT did not provide better recovery than an equal dose of usual therapy.¹³ These and other findings highlight that not everybody has the same set of physiological deficits after stroke, recovers in the same way or responds to the same form of therapy.¹⁴ Therefore, it is important to have a greater understanding of the mechanisms of recovery and whether a therapy is driving beneficial or maladaptive neuroplasticity.⁹⁻¹⁶

Progress towards better methods of upper limb rehabilitation after stroke needs to consider that clinical phenotype may be insufficient for targeting forms of task-specific therapy to those people most likely to benefit,¹⁷ and that restoring physiological function probably requires the development and application of rehabilitation therapies that promote activity-driven reorganisation of neural networks spared by the stroke¹⁸ and consideration of the characteristics of the individual.¹⁹ For example, non-primary cortical motor regions, including premotor and supplementary motor areas, show adaptation associated with improvement in movement performance.^{18,20} This adaptation is most evident in people with greater damage to the corticospinal system.^{21,22} In terms of predictive markers, there are experimental, non-trial indications that baseline, before therapy, brain activity in the primary motor cortex during movement²³ and the amount of damage to descending motor white matter pathways²⁴ at baseline (i.e. before therapy) may be related to recovery in response to therapy. Accordingly, rehabilitation trials need objective, sensitive neural measures to understand how a therapy produces benefit (mechanisms) and which people are likely to respond (predictive markers).^{14,15,17,18,25} Proof of concept of this approach is provided by investigations into language recovery.²⁶ Gaining this greater understanding will identify the mechanisms that should be targets for therapy and add information to algorithms designed to aid therapists to provide the most appropriate therapy for individuals²⁷ (www.viatherapy.org).

Realistically, if we are to incorporate mechanism and predictive marker data into accurate models to inform clinical decision-making then larger sample sizes are clearly required. Embedded in the trial reported here are objective neuroimaging and neurophysiological measures of participants' residual motor neural network before and after a 6-week treatment period.

The specific forms of physical therapy employed in the trial reported here were functional strength training (FST) focused on improving ability to perform everyday functional tasks, and movement performance therapy (MPT) focused on enhancing quality of movement required for everyday functional tasks [called extra conventional physical therapy (CPT) in our previous early-phase trial].²⁸ FST is based on evidence from experimental and clinical studies of benefit for people with substantial to moderate paresis early after stroke.^{28–34} It forms part of the CPT provided in routine clinical practice. MPT is the component of routine CPT that is focused on enhancing the quality of the movements required for the performance of everyday functional tasks.^{28,35–38} Such conceptually different physical therapies have been found in a meta-analysis to be no more or less effective than each other.³⁹ However, in both of our early-phase trials we found marked variation within people in their response to MPT and to FST.^{28,35} Thus, a comparison of the clinical efficacy FST and MPT was used in the trial reported here as the context for investigating the predictors of response to and mechanisms of action to specific physical therapies.

Objectives

The scientific driver for this trial was that detailed understanding of the interaction between the treatment and each patient's residual neural function will more likely enable physical therapies to be targeted at recovery mechanisms in those stroke survivors most likely to respond. The specific objectives were to:

1. determine if upper limb motor recovery is enhanced more by FST + CPT than an equal dose of MPT + CPT commenced early after stroke
2. identify the similarities and differences in the neural correlates of clinical improvement in upper limb motor function in response to (1) FST + CPT and (2) MPT + CPT
3. determine whether or not any pretreatment neural characteristics or combination of (1) anatomical location of infarction, (2) volume of the stroke lesion, (3) residual structural corticocortical connectivity, (4) residual corticospinal connectivity and (5) brain–muscle functional connectivity [derived from Transcranial Magnetic Stimulation (TMS)], are sufficiently predictive of upper limb recovery after stroke to enable physical therapy to be targeted at those people most likely to respond.

Achieving these objectives before undertaking a Phase III randomised controlled trial (RCT) conforms with the Medical Research Council (MRC) Framework for Design and Evaluation of Complex Interventions to Improve Health.⁴⁰

Chapter 2 Randomised controlled trial: methods

Design

A randomised, controlled, observer-blind, two-group, multicentre trial. The randomisation order was generated before the trial began and allocation was via an independent telephone interactive voice response randomisation service. Clinical efficacy measures were made before randomisation (baseline), the working day (± 7 days) after the 6-week intervention ended (outcome) and 6 calendar months (± 14 days) after the index stroke (follow-up). Neural measures were made at baseline and outcome within 10 days following the clinical efficacy measures. All assessors were blinded at baseline as randomisation had not yet occurred. At outcome and follow-up all assessors were, where exceptional events did not dictate, blinded to the randomisation. When at all possible, randomised participants were included in outcome and follow-up measures. The trial procedure is illustrated in *Figure 1*. The trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and covers all the CONSORT checklist items.

Trial registration

The trial was registered on Current Controlled Trials with the unique identifier ISRCTN19090862 (www.controlled-trials.com). In addition, the protocol was published⁴¹ and the study was adopted by the

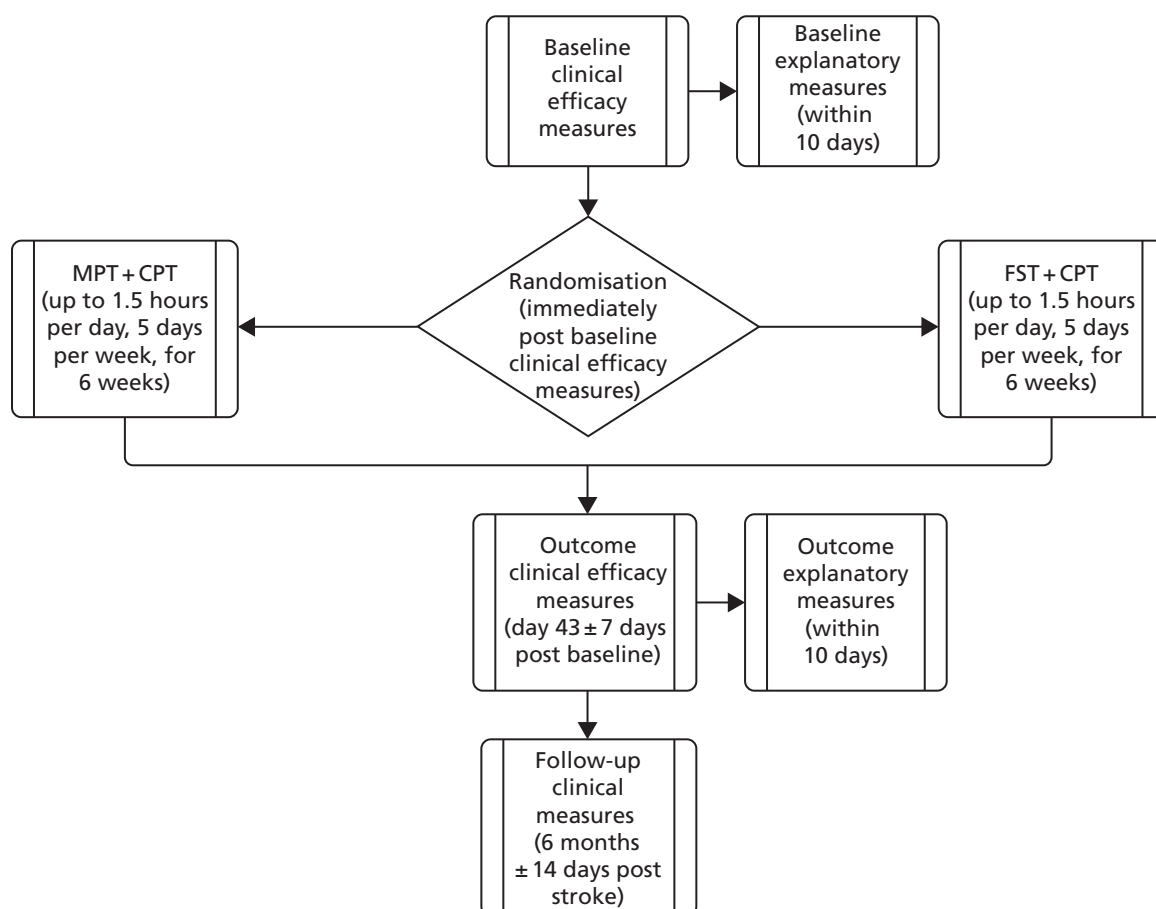


FIGURE 1 Flow chart to illustrate trial procedure.

UK Clinical Research Network and, therefore, appeared on the UK Clinical Research Network Study Portfolio.

Ethics and research governance approval

The Norfolk Research Ethics Service provided ethics approval on 22 February 2012 (reference number 11/EE/0524). All participants provided informed consent.

The trial was outside the scope of the Clinical Trials Directive defined by the Medicines and Healthcare Products Regulatory Agency as neither trial intervention included provision of a pharmacological compound.

The University of East Anglia (UEA) was the recipient of the funding. UEA together with the University of Glasgow Clinical Trials Unit [Robertson Centre for Biostatistics (RCB)] and the Norwich Clinical Trials Unit was responsible for the organisation and running of the trial. UEA had subcontracts with each partner university that laid out the delegated responsibilities of the partner and funding to be provided. Each partner university was responsible for procuring suitable management and governance provision with their local NHS trust centres. All members of the trial team had current good clinical practice (GCP) training. Those members of the trial who were actively involved in clinical contact with participants but were not employed by the NHS had either honorary clinical contracts or research passports.

All decisions regarding eligibility for entry, provision of written informed consent, inclusion, exclusion and attrition were documented as per the MRC Code of Good Practice in Clinical Trials and the CONSORT guidelines. Relevant trial documentation will be retained for a period of 10 years after the end of data collection to comply with the GCP regulations and to ensure availability of data for any subsequent systematic reviews and meta-analyses. The UEA will archive trial documents in a secure facility. The custodian will be Professor Pomeroy.

Participants

The combined inclusion and exclusion criteria for potential participants were people:

- (a) with a clinical diagnosis of stroke in the territory of the anterior cerebral circulation, cortical and/or subcortical as corroborated through routine clinical imaging
- (b) aged ≥ 18 years
- (c) who were between 2 and 60 days after stroke when providing informed consent
- (d) were able, before the index stroke, to use the paretic, contralesional, upper limb to lift and then drink from a cup
- (e) who were defined as medically stable as confirmed by the stroke service medical team responsible for the individual's stroke care
- (f) with enough voluntary muscle contraction in the paretic upper limb to score at least 11 of the 33 points on the Motricity Index pinch section⁴²
- (g) who were unable to complete the Nine-Hole Peg Test (9HPT) within 50 seconds⁴¹
- (h) with a score of 0 or 1 on the Extinction and Inattention subscale of the National Institutes of Health Stroke Scale (no obvious spatial neglect)
- (i) who could imitate action with the non-paretic (ipsilesional) upper limb. The research therapist sat alongside a potential participant to demonstrate five upper limb activities. The potential participant was asked to watch and then perform the activities. The accuracy of imitation was assessed on the 3-point scale used by Decety: 2 = correctly reproduced action, 1 = incorrectly reproduced action and 0 = not reproduced.⁴³ Those people scoring 8 out of 10 or above were considered as able to imitate and, therefore, eligible for inclusion in this trial.

Settings for recruitment, assessment and treatment

- Birmingham (centre 1).
 - Moseley Hall Hospital, Birmingham Community Healthcare NHS Trust.
 - Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust.
 - University of Birmingham Imaging Centre.
 - Participants' own homes.
- Norfolk (centre 2).
 - Acute Stroke Unit, Norfolk and Norwich University Hospital NHS Trust.
 - Stroke Rehabilitation Ward, Mulberry Unit, and Early Supported Discharge Team, Norfolk Community Health and Care NHS Trust.
 - James Paget University Hospitals.
 - The Movement Analysis Laboratory at the UEA.
 - Participants' own homes.
- North Staffordshire (centre 3).
 - Haywood Hospital, Staffordshire and Stoke-on-Trent Partnership NHS Trust.
 - University Hospital of North Midlands NHS Trust.
 - Participants' own homes.

Screening and recruitment of participants

Potential participants were screened from the three centres and followed up on the condition that research governance and ethics approvals were in place for that setting. A two-stage screening process was used because some study criteria required movement assessment expertise that was not always present in the Comprehensive Local Research Network (CLRN) screening teams.

Stage 1 of the screening process was conducted by CLRN research nurses in liaison with stroke service clinical nurses and therapists. They screened for study criteria (a)–(f) as described in *Participants (Figure 2)*. For some potential participants, the screening happened more than once. This was because medical and functional characteristics change over time after stroke so if somebody was unsuitable on one occasion it was possible that they could change and meet the trial criteria later. An individual's progress was monitored until eligibility for this trial was clear (*Figure 3*). At the end of stage 1, informed consent was taken by either CLRN nurses or research therapists (enrolment). All people screened were categorised as unsuitable, refused informed consent, or provided informed consent.

People providing informed consent undertook stage two of the screening process with a research therapist to ascertain concordance with study criteria (g), (h) and (i) (*Figure 4*). Those people who did not meet all three of the inclusion criteria were reassessed later if they agreed and the exclusion time limit had not been met. At the end of stage 2 individuals were categorised as unsuitable for the trial or as a recruited participant.

Randomisation

Before the trial began, the computer-generated randomisation sequence was created by an independent statistician at the Glasgow Clinical Trials Unit. Participants were allocated to FST + CPT or MPT + CPT in a 1 : 1 ratio, stratified by (1) time after stroke (up to 30 days or 31–60 days); (2) ability to use the paretic upper

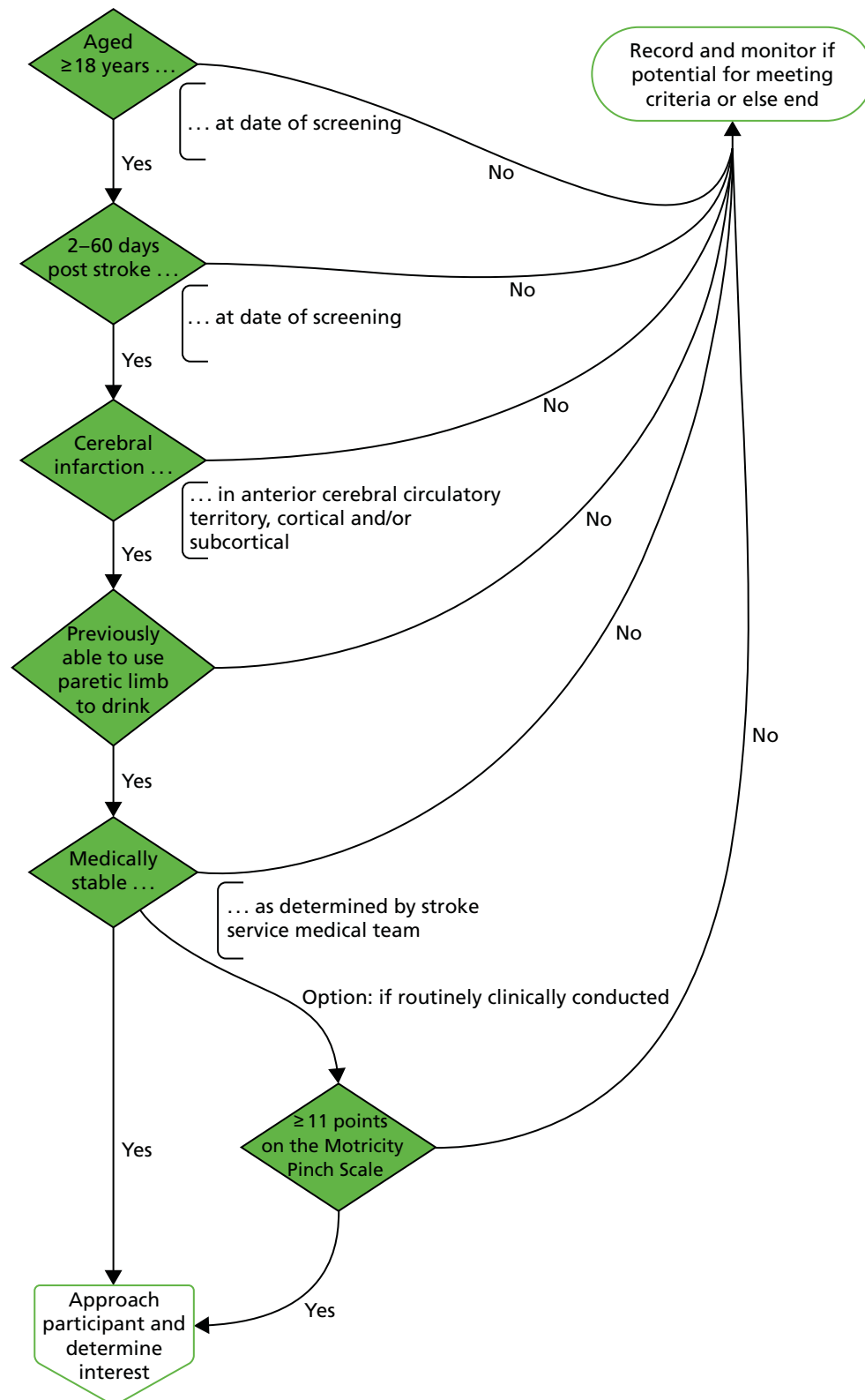


FIGURE 2 Stage 1: initial screening.

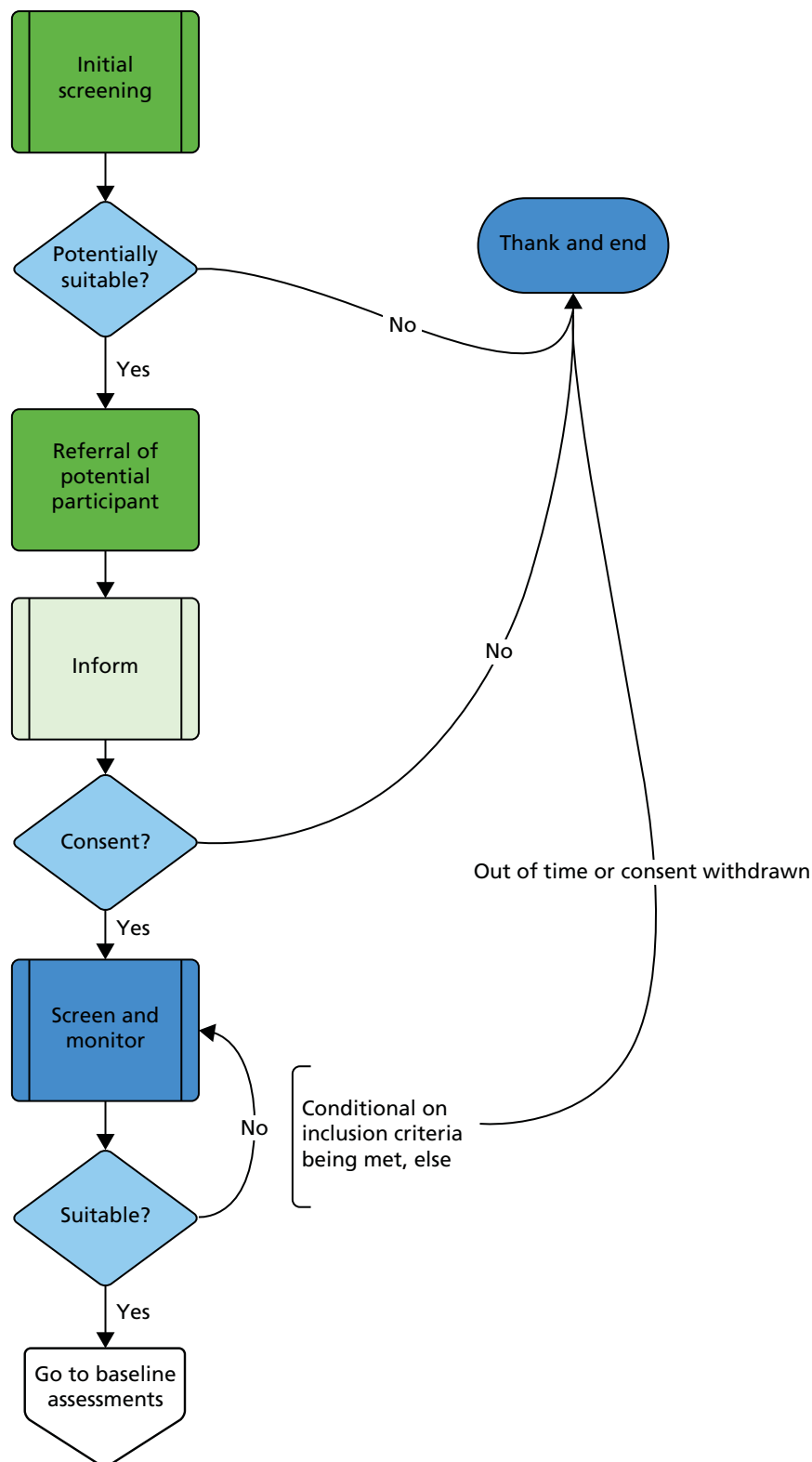


FIGURE 3 Stage 1: participant eligibility pathway. Dark green indicates clinician or research network colleague, light green indicates research network colleague or researcher, dark blue indicates researcher and light blue indicates participant.

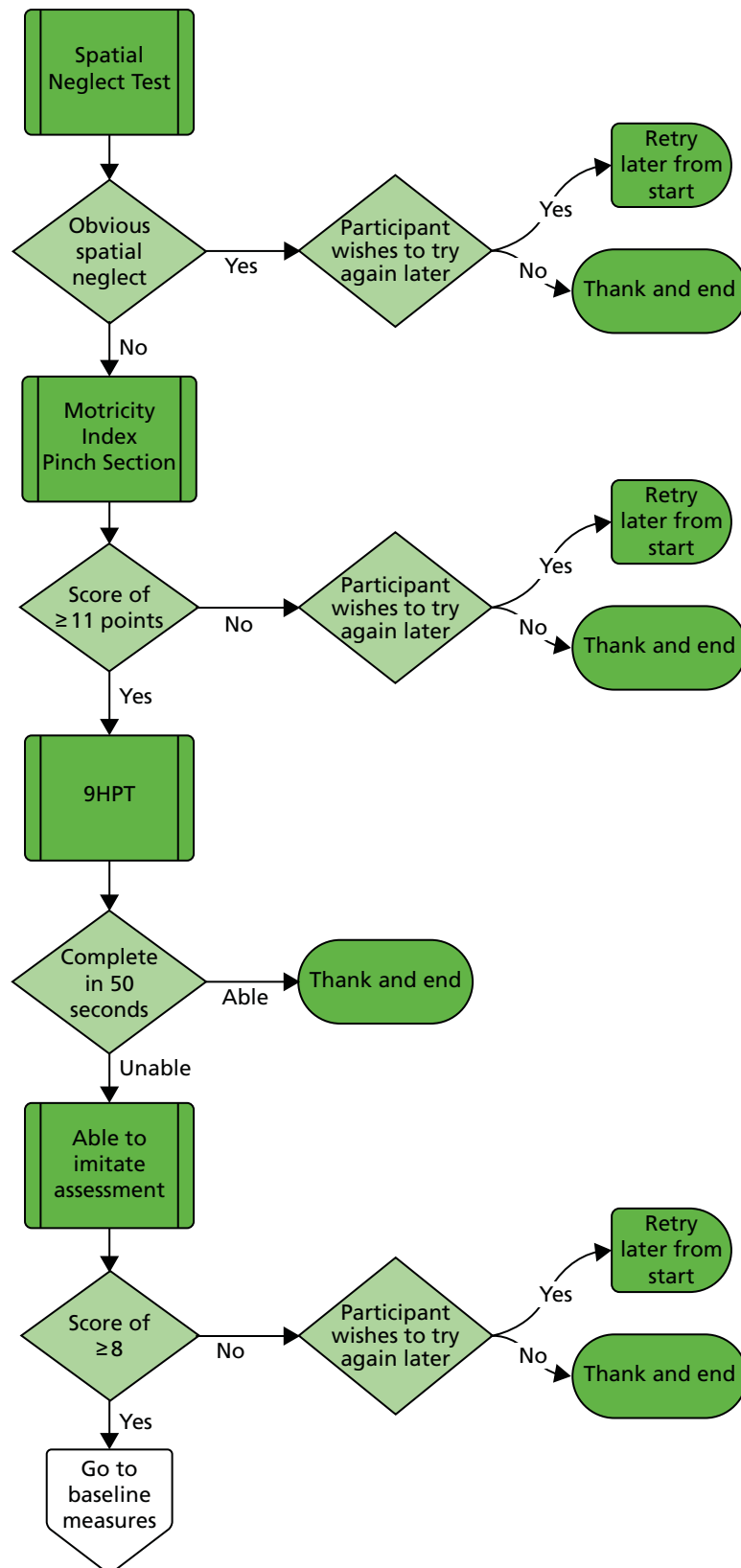


FIGURE 4 Stage 2: post-consent suitability assessment. Dark green indicates researcher and light green indicates participant.

limb as assessed by the 9HPT, moving one peg or less in 50 seconds, or moving 2–8 pegs in 50 seconds; and (3) clinical centre. An independent telephone randomisation service was used to conceal group allocation order from investigators, research therapists and blinded assessors prior to the randomisation of a participant. The telephone randomisation service was contacted by the team member (research therapist or blinded assessor) immediately after they had completed the baseline measures with a participant.

Sample size and power

The sample size calculation that was used accounted for the expected clustered data structure (patients within therapist within treatment group).⁴⁴ This sample size calculation was based on actual ARAT score data from our previous early-phase trial²⁸ and the expectation that the intraclass correlation coefficient (ICC) would be somewhat lower than 0.05 for patient outcomes.⁴⁵ On the assumption of an ICC of 0.01 in both treatment arms and three centres with a separate therapist for each randomised arm, a sample size of 99 participants per group would provide 80% power to detect a clinically important mean difference of 6.2 points in ARAT score change for data analysis using a two-sample *t*-test, with Satterthwaite correction, applying a 5% two-sided significance level and allowing for potentially different standard deviations (SDs) in the CPT + MPT (SD 7.9) and CPT + FST (SD 19.3) groups.

To account for clustering in the design (participants within a therapist within randomised treatment at each study site), a sample size inflation factor $1 + (m - 1) \times \text{ICC}$ was applied, where *m* is the cluster size and ICC uses SSC software version 1 (Health Services Research Unit, University of Aberdeen, Aberdeen, UK). On the assumption that recruitment would be distributed evenly across therapists, the sample size was therefore inflated to 129 evaluable participants per group. To allow for an attrition rate of 10% (7% in our previous single-centre trial)²⁸ we recruited 144 participants per group. The total sample size was 288.

Description of interventions

Therapy as usual, conventional physical therapy

All participants continued to receive their usual CPT provided by the clinical therapists. The CPT as delivered in the centres for the trial combined hands-on techniques emphasising postural alignment and quality of movement (an aspect of MPT) with goal-orientated task-specific training (an aspect of FST). The content and amount of CPT delivered to participants was recorded by the clinical therapists each day on a standardised form (see *Appendix 1*)⁴⁶ in accordance with the explanatory manual used in our earlier trials.^{28,35} The clinical therapists providing CPT were trained before the trial began. In addition, researchers provided regular reminders of the rationale for, and importance of, recording CPT and worked with clinicians around using the treatment schedule focused on queries that arose during the trial. Clinical therapists chose the CPT that they considered appropriate for participants. Whenever possible, the completed CPT forms were collected each week by a member of the research team. When not possible, these forms were stored with the clinical records until completion of the intervention phase and then collected by a member of the research team.

Trial interventions

The trial interventions were MPT and FST as described in the succeeding subsections.

Research therapists were assigned and trained to provide either FST or MPT. Clinical staff were not told which research therapist was assigned to provide which trial intervention so that the potential for bias in the provision of clinician-delivered CPT was minimised. However, this possibility cannot be eliminated completely as allocation to different types of exercise therapy is not as concealable as, for example, allocation to an active or placebo pharmaceutical compound.

Both trial interventions were provided for participants by a research therapist for up to 90 minutes per day, up to 5 days a week, for up to 6 weeks. It was anticipated that the trial interventions would not be provided (1) when a participant was unwell, (2) on the day of a trial assessment (e.g. MR scan), (3) when a participant was unavailable because of holiday or other personal reasons or (4) when there was a UK public holiday. If a session was missed then the reason for this was recorded. Participants received therapy both with the therapist physically present (direct contact) and during practice of activities prescribed as 'homework' by the research therapist (non-direct contact).

Training in delivering MPT and FST was provided for the research therapists before the first participant was recruited (see *Appendix 2*). All research therapists attended this training. If a therapist started during the trial then their training was completed before their first participant was randomised. In addition, two training update days were held during the trial for those therapists employed at that point. Through these update days, the within-trial research therapist networking was maintained and enhanced. This network enabled research therapists to consult regularly with their peers from different centres providing the same trial intervention to talk through understandings and practice. The trial manager, Dr Sue Hunter, and Professor Valerie Pomeroy were also involved in these networking conversations. Fidelity to intervention protocols was also assessed when Dr Sue Hunter and Professor Valerie Pomeroy made visits at short notice to accompany research therapists during a treatment session. Notice had to be given because it was essential to gain agreement from participants concerned. The purpose of training and monitoring was to minimise potential deviation from intervention protocols and difference between centres.

Trial intervention: movement performance therapy

The hands-on and sensory stimulation components of CPT that focus on restoring movement quality (i.e. efficient, smooth, timely, co-ordinated movement with normal alignment or symmetry of body structures prior to retraining functional movement) can be termed MPT.³⁶ MPT is 'therapist dependent', particularly when there is limited voluntary muscle activation; the therapist monitors and provides intrinsic feedback on movement performance through skilled observation, handling and facilitation techniques. Therapist-led hands-on guidance and feedback assists practice of functional tasks. Trial MPT emphasised interventions provided by a therapist using facilitation and guiding movement (therapist dependent) to provide sensory input to optimise joint alignment in preparation for voluntary movement (see *Appendix 3*). Some iterative practice of functional tasks was included but without systematic progression in resistance to movement or repetition.

Trial intervention: functional strength training

Functional strength training was provided according to a treatment schedule consisting of standardised therapy activities.⁴⁷ An online supplement to the published paper provides full details⁴⁷ in accordance with the TIDieR (Template for Intervention Description and Replication) guidelines.⁴⁸ In summary, FST is repetitive progressive resistive exercise during goal-directed functional activity, with the therapist providing verbal prompting and feedback. Hands-on intervention is not provided other than that required to maintain safety (e.g. prevent a fall). FST focuses on improving the power of shoulder/elbow muscles for appropriate placing of the hand for the task being practised, the production of appropriate force in the arm and hand muscles to achieve the specific grasp, and manipulation of everyday objects. Initially, the resistance level is the maximum load that permits five repetitions of the task being practised. Systematic progression uses repetition and increased resistance. Content of FST is divided into (1) specific movements for muscle groups (e.g. emphasis on elbow flexion/extension), (2) upper limb gross movement patterns underlying functional activity (e.g. shoulder flexion/external rotation and elbow extension to reach forward), (3) hand reaching/retrieval activity (e.g. reaching to grasp something on a shelf while seated), (4) hand grip activities, (5) hand manipulation involving entire everyday movements and (6) using objects such as screw top canisters, pegs, food items (e.g. bag of dried pasta), mugs and pens. These activities are extended into more complex everyday activities such as using the paretic upper limb to place different food items into a shopping bag and then lift the bag onto a shelf, and open a bottle and drink from it and pour tea from a pot. The therapist provides feedback and instructions that encourage an external focus of attention (e.g. whether or not the teapot has been lifted off the table) rather than focusing on the arm/hand (e.g. amount of shoulder movement when lifting the teapot).

and informative verbal feedback on performance on at least 50%, but less than 100%, of attempts to encourage self-evaluation for motor learning.

Measurement battery

Clinical efficacy measures: objective 1

For the clinical efficacy measures (objective 1) participants were seated in an upright chair, except for some items of the Wolf Motor Function Test (WMFT), which allows for a posture in which knees, hips and ankles are maintained at 90°. A table was available so that, when appropriate for the measurements, the forearms were supported on the table with elbows directly below the glenohumeral joint at the start of an item of the WMFT. Measures pertain to the contralesional upper limb (paretic).

The primary outcome measure was:

- The Action Research Arm Test (ARAT), which has four subsections (grasp, grip, pinch and gross movements). Within each subsection are three to six items scored from 0 (unable) to 3 (normal performance), giving a total possible score of 57.⁴⁹ The ARAT is a measure of the primary focus of both interventions (i.e. improved upper limb function).

The secondary outcome measures were:

- The WMFT, which is a valid and reliable assessment with 15 items designed for use with stroke survivors and is complementary to the ARAT. It measures quality of movement during 15 functional tasks including both simple actions (e.g. placing forearm on table) and complex tasks (e.g. turning key in a lock).^{50,51}
- Hand Grip and Pinch Grip Force tests using a myometer held securely on a stable surface. The upper limb position for both pinch and grip force was standardised⁵² and the myometer was set to 'zero' after the subject was positioned with their hand/digits around the bars, 'at rest'. Force values were obtained during three trials for which participants were instructed to 'squeeze as hard as you can'. The maximum value was used for data analysis.

Neural measures: objectives 2 and 3

Participants were studied twice: at baseline and at outcome (see *Design*). The trial team had systems in place to maintain consistency and data quality across sites and to treat multicentre data appropriately. Full training was given to all trial centre teams.

Once testing began, data from all sites were promptly sent to the University of Oxford team for rigorous quality control prior to processing to extract relevant values. Quality control assessments included manual checks (e.g. subject motion) and automated checks (e.g. signal-to-noise ratio, motion correction parameters and range checks).

To maximise recruitment to and minimise attrition from neural measures, we provided participants with full explanations and opportunities to ask questions and plenty of time to be made comfortable and to practice the tasks.

The neural measures were:

1. The anatomical overlap of the stroke lesion with the corticospinal tract [Montreal Neurological Institute (MNI) CST – yes/no]. This variable identifies whether or not the lesion overlaps with a mask approximating the CST. The CST mask was defined using tractography in a group of control brains in standard space to track between motor cortex and medullary pyramids. The lesion was delineated manually on each patient's T1-weighted 1 × 1 × 1 mm brain image using FSL view, an image viewing

- tool available within the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's (FMRIB) Software Library (FSL). Overlap between the lesion volume and the CST was determined by overlaying the lesion mask with the CST mask.
2. The volume of the stroke lesion (lesion volume mm³). This variable was determined by calculating the volume of the manually defined stroke mask described for (1).
 3. Corticocortical anatomical connectivity as per fractional anisotropy (FA) from corpus callosum midline (FA MNI corpus callosum midline – range = 0–1). Diffusion tensor imaging data were first corrected for head motion and eddy current using tools from FSL. A diffusion tensor model was then fitted to the pre-processed data to calculate voxel-wise values of FA. Mean FA from within a standard space region of interest, incorporating the whole corpus callosum on a midline brain slice, was calculated.
 4. Corticospinal anatomical integrity as per asymmetry of CST FA (ipsilesional-to-contralesional ratio MNI CST – range = –1 to 1). Regions of interest on a single slice at the level of the internal capsule were created to provide masks estimating the location of the CST. Mean FA from within these masks was calculated. A ratio of ipsilesional-to-contralesional values was calculated.
 5. Corticospinal functional connectivity as per presence or absence of a resting motor-evoked potential (MEP) for biceps brachii muscle in paretic upper limb (yes/no). Single pulses of TMS using a standard 70 mm figure-of-eight coil were given over the hand/arm area of primary motor cortex of the ipsilesional hemisphere and then the contralesional hemisphere. MEP data were recorded and processed using electromyography data collection software. Resting motor threshold (RMT) was defined as the stimulator output that produced > 50 μ V in 5 out of 10 trials.⁵³
 6. Corticospinal functional connectivity as per presence or absence of a resting MEP for the extensor carpi radialis muscle in the paretic (contralesional) upper limb (yes/no). Data were processed as for (5).
 7. The RMT in paretic biceps brachii (pBB) when MEP was present (percentage). Value extracted was the lowest percentage output of the stimulator at which a MEP was present.
 8. The RMT in paretic extensor carpi radialis when MEP was present (percentage). The value extracted was the lowest percentage output of the stimulator at which a MEP was present.

Adverse reactions and adverse events

Participation in FST and MPT is considered low risk for adverse events (AEs). However, there is a small possibility that either therapy could be associated with an overuse syndrome, expressed as experience of pain or fatigue. These were therefore classified as potential adverse reactions as follows:

- Pain was considered an adverse reaction if (1) a participant reported onset or increase of paretic upper limb pain (verbally or behaviourally), (2) the pain was sustained over four consecutive therapy sessions and (3) the clinical team were unable to account for this in any other way than involvement in the trial. If pain occurred then the research therapist adjusted the trial therapy as appropriate or, if indicated, stopped it on either a permanent or temporary basis. The date of the adverse reaction was recorded as the date of the fourth therapy session.
- Fatigue was considered to have occurred if (1) a participant demonstrated a decrease of two levels in the Motricity Index upper limb score on two consecutive therapy sessions and (2) the clinical team could not account for this in any other way than involvement in the trial. This was addressed by the therapist adjusting the trial therapy as appropriate or, if indicated, stopping the trial therapy on either a permanent or temporary basis. The date of the adverse reaction was recorded as the date of the second therapy session.

To report serious adverse events (SAEs), the trial team used the Norfolk and Norwich University Hospital and UEA joint standard operating procedure (SOP). The latest version can be found www.nnuh.nhs.uk/Dept.asp?ID%20=%20681 (see SOP 205). All SAEs were assessed by the local principal investigator, countersigned by the chief investigator, reported to the sponsor and reported to the Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC). All SAEs were followed up until a

documented end date and resolution could be provided, or the participant ended the trial. Participants were considered to have reached the end of the trial when the first of the following occurred:

- completion of assessment at 6 months after stroke
- withdrawal of consent
- SAE resulting in withdrawal of participant or death
- loss to follow-up.

If a SAE was still ongoing at the time a participant reached a trial end point, their trial end date was also used to record their SAE end data.

Statistical analysis

The statistical analysis plan (SAP) was agreed, signed and dated prior to the database lock and unblinding of the treatment allocations (see *Appendix 4*).

There was a change to the original analysis plan from taking account of clustering by therapist to only adjusting for the study site. The change was made because, for practical reasons, the participants were not clustered within the same therapist for all their sessions.

Clinical efficacy (objective 1)

To address objective 1 the primary analysis compared the change in the efficacy parameters (baseline and outcome) between the treatment groups. Change in the efficacy parameters (ARAT, WMFT, and Hand Grip Force and Pinch Grip Force tests) at outcome were analysed using analysis of covariance (ANCOVA) models adjusted for the baseline value and randomisation strata (time after stroke, ability to use paretic upper limb, clinical centre). Adjusted least squares mean difference and 95% confidence intervals (CIs) were reported. When the outcome distribution deviated from a normal distribution, a log or other appropriate transformation was applied.

Neural correlates of clinical improvement (objective 2)

To answer the second objective, associations between the changes in neural variables were compared with the changes in clinical efficacy measures (baseline to outcome). Correlation coefficients were calculated for the two treatment groups separately and for the groups combined.

Predictive neural markers of clinical improvement (objective 3)

The third objective was answered through subgroup analysis of the change in ARAT score at outcome. For each baseline covariate being investigated as a potential predictive marker of clinical improvement, the treatment effect was calculated within each level of the subgroup (adjusted as for the first objective) and an interaction term between randomised treatment and baseline covariate was included in the model.

Trial management

Data collection

All data were collected in accordance with trial operating procedures. These were developed to the standards required in the SOPs of the Norwich Clinical Trial Unit.

Case report forms (CRFs) were developed to enable capture of primary and secondary outcome data at the time points of baseline, outcome and follow-up. In addition, the CRFs recorded demographic information such as sex and type of stroke. Throughout the trial, the completed CRFs were secured in a locked filing cabinet in a research office in the Moseley Hall Hospital (Birmingham), the Queen's Building at the UEA (Norfolk), or the Haywood Hospital (North Staffordshire). Once the follow-up phase of the trial was

completed, all CRFs were moved securely to the UEA for final data query resolution, in preparation for the final database lock. All CRFs were then securely stored and archived at the UEA.

Data entry and quality assurance

The study database was set up and managed by the Data Management Team at Glasgow Clinical Trials Unit. The data management plan is included as *Appendix 5*. Data management included:

- design and specification of the database and data entry system
- real-time validation of data entry for data types and ranges
- provision of a double data entry and checking system at the end of the study
- import of data
- data queries for validation at end of study
- database lock
- data set extraction for analysis.

Procedures were developed, implemented and monitored to maintain blinding and limit access of members of the research team to data throughout the trial. Data were sent to the RCB for entry and quality control in a secure standardised manner in keeping with the Data Management Plan produced by the RCB (see *Appendix 5*). The RCB was responsible for accumulating, reviewing and reporting on data from several primary and secondary sources.

Primary data sources were from paper copies of study CRFs completed at study site.

Secondary data sources were from (1) database amendment requests and (2) responses to data queries.

External data sources included the results of the TMS and magnetic resonance imaging (MRI) tests/procedures.

Trial Steering Committee

A TSC was convened to provide overall supervision and ensure good conduct of the trial (e.g. adherence to the Declaration of Helsinki and good practice in user involvement). This was undertaken by nominating potential members to the Efficacy and Mechanism Evaluation (EME) programme board, which then appointed people to the TSC. Members of the TSC were:

- Professor Anne Forster (independent chairperson)
- Professor Christopher Weir (collaborator, statistician and methodologist)
- Dr Sue Hunter (collaborator, principal investigator)
- Professor Jon Marsden (independent member)
- Professor John Rothwell (collaborator, TMS lead)
- Professor Valerie Pomeroy (chief investigator)
- Dr Ailie Turton (independent member)
- Ms Emma Costello (clinical research administrator)
- Mr Nick Leavey (clinical trial manager).

The TSC met on 22 November 2012, 23 May 2013, 27 August 2013, 11 December 2013, 6 February 2014, 3 July 2014, 27 February 2015, 11 April 2016 [a full meeting was not convened on request of independent chairperson (AF); however, an up-to-date trial progress report was distributed to the TSC and comments were subsequently shared and responded to by e-mail] and 5 December 2016 (a final TSC meeting to review the final Robertson Centre Report and the current draft monograph).

Data Monitoring and Ethics Committee

The DMEC reported directly to the chair of the TSC. Members of the DMEC appointed by the EME programme were:

- Professor Sally Singh (independent chairperson)
- Professor Gert Kwakkel (independent member)
- Dr Martyn Lewis (independent member)
- Professor Valerie Pomeroy (chief investigator)
- Dr Andrew Walker (until 31 December 2014) (clinical trial manager)
- Nick Leavey (from 3 September 2014) (clinical trial manager).

The DMEC met on 16 July 2013, 29 January 2014, 16 July 2014, 2 February 2015, 2 September 2015 and 25 November 2016.

Public and Patient Involvement

At the beginning of the trial, the initial trial manager and Professor Pomeroy attempted to secure a Patient and Public Involvement (PPI) representative through the Patient and Public Involvement in Research (PPIRes)⁵⁴ group. An early version of the protocol for the grant application was reviewed by PPIRes. Unfortunately, however, no one was identified by PPIRes to be the PPI representative for this trial.

Nonetheless, PPI has still taken various forms throughout the trial. From the outset, the trial featured at meetings of the Norfolk Community Health and Care NHS Trust patient and carer groups, in Norwich. The trial team therefore benefited from PPI comments and suggestions on a range of elements, particularly the development of participant information resources.

Further PPI was also explored by Dr Andrew Walker via a contact provided by the EME programme manager. This did not lead to further PPI. Therefore, a replacement PPI representative was not identified at this point in the trial.

As outlined in the progress report submitted on 1 April 2015, a PPI representative was identified from Headway Suffolk. The person identified was Helen Fairweather, the chief executive officer of Headway Suffolk, who kindly agreed to be a member of the TSC. Since April 2015, Helen has been invited to all TSC meetings and sent copies of the agendas and subsequent minutes and associated documents.

A participant thank-you event was held at the Norwich Community Hospital on 3 May 2016. The event was to celebrate the trial achieving its 288-participant recruitment target. Over 50 local participants attended, who were provided with a verbal report on the remaining ongoing trial activity and plans for dissemination of the trial results. All were appreciative of their involvement in the trial and comments were received in approval of the dissemination plan.

During the trial, and following a substantial amendment (eighth amendment), three editions of a FAST INDICATE participant newsletter were distributed to trial participants to keep them updated on trial progress and its planned dissemination.

Chapter 3 Results: clinical efficacy

Objective addressed

To determine if upper limb motor recovery is enhanced more by FST + CPT than an equal dose of MPT + CPT commenced early after stroke.

Dates of recruitment and follow-up periods

Screening for potential participants started on 1 April 2012 and ended on 25 January 2016. The first participant was randomised on 17 October 2012 and the last participant was randomised on 29 January 2016. The last follow-up assessment, at 6 months after stroke, was 6 July 2016.

Participant characteristics

The characteristics of participants are detailed in *Table 1*. In summary, the mean age (SD) of participants in this trial was 72.2 (12.5) years. The sex distribution was 64.6% male and 35.4% female. Informed consent was given within 30 days of stroke by 59% of participants and at ≥ 31 days by 41%. All participants had been diagnosed with stroke in the territory of the anterior cerebral circulation. The stroke was caused by a haemorrhage for 8.7% of participants and by ischaemia for 91.3%. The right-hand side of the body was more affected by the stroke than the left-hand side for 42% of participants.

Flow of participants through the trial

The CONSORT flow chart for this trial in respect to the primary outcome (ARAT score) is provided in *Figure 5*. In summary, a total of 5064 stroke survivors were screened for eligibility for this trial. Of these, 2929 (58%) were excluded because they did not meet the initial study inclusion criteria, with a further 872 (17%) excluded for additional reasons, such as being outside the trial catchment area or having severe cognitive and/or language impairment. This left 1263 identifiable eligible people; however, 536 (42%) of these people declined to talk to the research team. The remaining 481 (38%) provided informed consent and undertook the trial suitability screening assessment; of those, 138 (29%) did not meet the eligibility criteria and a further 55 (11%) either withdrew consent or otherwise were not randomised. The remaining 288 were recruited as participants and randomised into the trial. Consequently, 288 participants undertook the baseline assessments and were subsequently allocated randomly to the MPT group ($n = 143$) or the FST group ($n = 145$).

At the primary end point of the outcome (at the end of the 6-week intervention phase), 245 (85.1%) participants undertook the primary measure (ARAT score), of whom 119 had been allocated to MPT + CPT and 126 to FST + CPT. Attrition reasons were:

- withdrew as a result of a SAE or AE (MPT + CPT, $n = 5$; FST + CPT, $n = 5$)
- unwilling to continue (MPT + CPT, $n = 6$; FST + CPT, $n = 6$)
- withdrew consent (MPT + CPT, $n = 4$; FST + CPT, $n = 2$)
- lost to outcome/other (MPT + CPT, $n = 5$; FST + CPT, $n = 3$)
- did not attend for assessment, but remained in trial (MPT + CPT, $n = 4$; FST + CPT, $n = 3$).

TABLE 1 Participant characteristics, by treatment group and overall, at baseline

Characteristic	Treatment group		All (N = 288)
	FST + CPT (N = 145)	MPT + CPT (N = 143)	
Age (years), mean (SD)	71.9 (12.7)	72.4 (12.3)	72.2 (12.5)
Sex, n (%)			
Male	96 (66.2)	90 (62.9)	186 (64.6)
Female	49 (33.8)	53 (37.1)	102 (35.4)
Type of stroke, n (%)			
Ischaemic	131 (90.3)	132 (92.3)	263 (91.3)
Haemorrhagic	14 (9.7)	11 (7.7)	25 (8.7)
Side of brain lesion, n (%)			
Left	63 (43.5)	58 (40.6)	121 (42.0)
Right	82 (56.5)	85 (59.4)	167 (58.0)
9HPT at consent, n (%)			
≤ 1 peg	91 (62.8)	90 (63.0)	181 (62.9)
2–8 pegs	54 (37.2)	53 (37.1)	107 (37.2)
Days after stroke at consent, n (%)			
≤ 30 days	86 (59.3)	84 (58.7)	170 (59.0)
≥ 31 days	59 (40.7)	59 (41.3)	118 (41.0)
ARAT total score – paretic, mean score (SD) ^a	24.7 (18.9)	26.2 (17.4)	25.5 (18.2)
WMFT – performance, mean score (SD) ^b	36.4 (20.25)	37.6 (17.1)	37.0 (18.8)
Grip force (kg), mean score (SD) ^c	7.6 (8.7)	6.9 (8.1)	7.2 (8.4)
Pinch force (kg), mean score (SD) ^d	2.2 (2.2)	1.9 (2.3)	2.1 (2.2)

a Number of data sets available for analysis were: FST + CPT = 144; MPT + CPT = 139; and All = 283.

b Number of data sets available for analysis were: FST + CPT = 136; MPT + CPT = 129; and All = 265.

c Number of data sets available for analysis were: FST + CPT = 141; MPT + CPT = 139; and All = 280.

d Number of data sets available for analysis were: FST + CPT = 131; MPT + CPT = 133; and All = 264.

At 6 months after stroke, the follow-up time point, 208 (72.2%) participants undertook the primary measure (ARAT score), of whom 104 were allocated to MPT + CPT and 104 to FST + CPT. Attrition at the follow-up point had occurred for the following reasons:

- withdrew as a result of a SAE or AE (MPT + CPT, *n* = 15; FST + CPT, *n* = 8)
- unwilling to continue (MPT + CPT, *n* = 13; FST + CPT, *n* = 11)
- withdrew consent (MPT + CPT, *n* = 4; FST + CPT, *n* = 3)
- investigator withdrawal (MPT + CPT, *n* = 0; FST + CPT, *n* = 1)
- lost to outcome/other (MPT + CPT, *n* = 7; FST + CPT, *n* = 18).

Adverse reactions, adverse events and serious adverse events

No SAEs met the criteria for reporting to the National Research Ethics Service. All SAEs were reviewed by the DMEC. Only four participants experienced an adverse reaction of pain or fatigue during the intervention phase (*Table 2*).

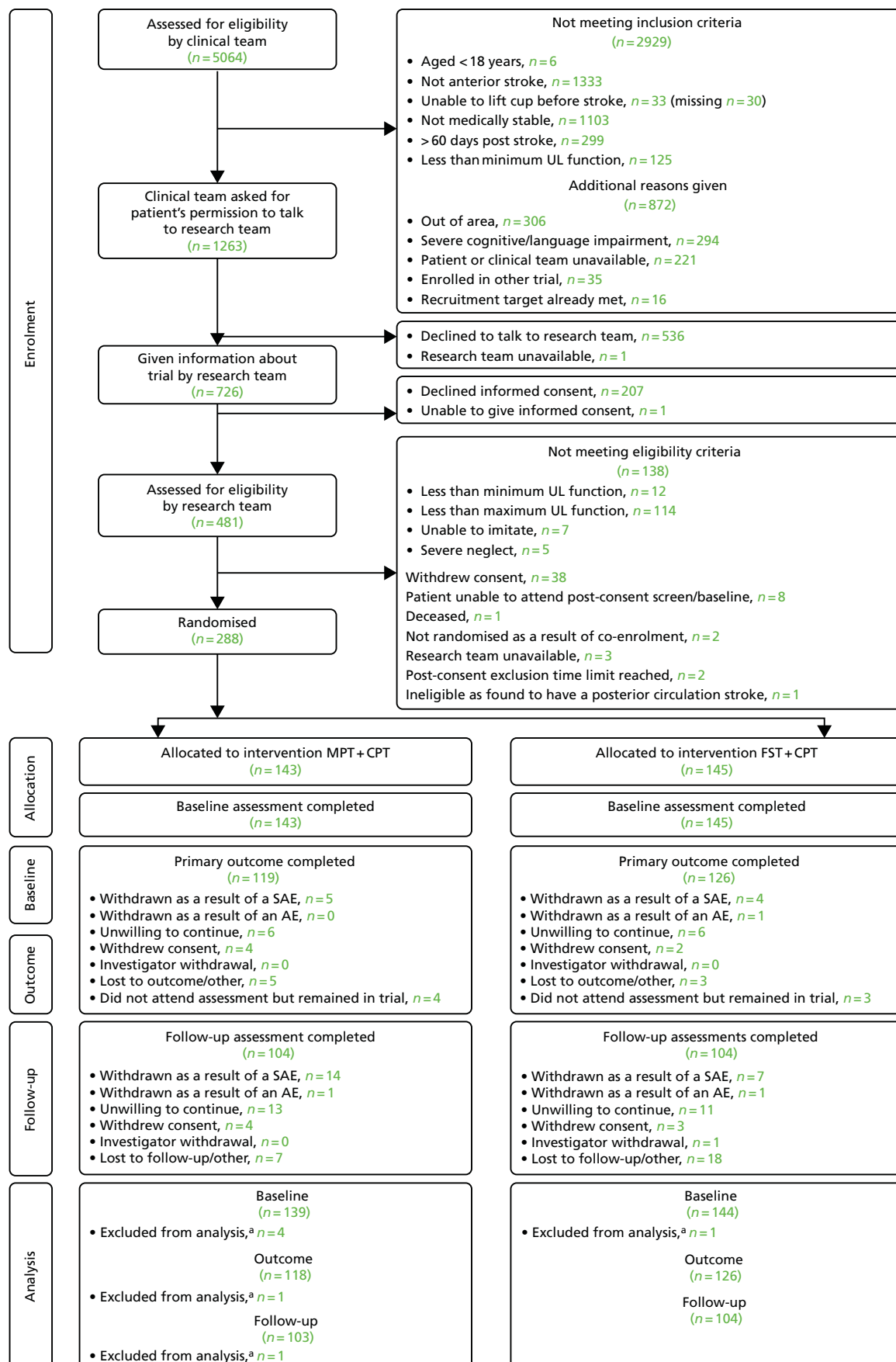


FIGURE 5 All centres: CONSORT 2010 flow diagram. a, Data are excluded from analysis if missing items prevent the ARAT total score from being calculated. UL, upper limb.

TABLE 2 Number of participants experiencing an adverse reaction during the treatment phase by treatment group and overall

Adverse reaction	Treatment group, <i>n</i> (%)		All (<i>N</i> = 288), <i>n</i> (%)
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)	
Any adverse reaction of pain	1 (0.69)	1 (0.70)	2 (0.69)
Any adverse reaction of fatigue	3 (2.07)	1 (0.70)	4 (1.39)

Adverse events, related AEs, SAEs and unexpected AEs during the intervention phase are detailed in Tables 3–6. No clinically important differences are detectable between the FST + CPT and MPT + CPT groups.

Those AEs, related AEs, SAEs and unexpected AEs that occurred during the follow-up phase are detailed in Tables 7–10. No clinically important differences are detectable between the FST + CPT and MPT + CPT groups.

TABLE 3 Number of participants experiencing AEs during the intervention phase, by treatment group (one participant may have experienced more than one event)

Adverse event	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	56 (38.62)	59 (41.26)
Injury, poisoning and procedural complications	18 (12.41)	19 (13.29)
Infections and infestations	17 (11.72)	7 (4.90)
Musculoskeletal and connective tissue disorders	11 (7.59)	11 (7.69)
General disorders and administration site conditions	11 (7.59)	8 (5.59)
Nervous system disorders	8 (5.52)	8 (5.59)
Gastrointestinal disorders	4 (2.76)	6 (4.20)
Vascular disorders	1 (0.69)	8 (5.59)
Psychiatric disorders	5 (3.45)	1 (0.70)
Respiratory, thoracic and mediastinal disorders	1 (0.69)	4 (2.80)
Cardiac disorders	1 (0.69)	3 (2.10)
Renal and urinary disorders	2 (1.38)	1 (0.70)
Eye disorders	0 (0.00)	2 (1.40)
Immune system disorders	1 (0.69)	1 (0.70)
Investigations	0 (0.00)	2 (1.40)
Ear and labyrinth disorders	1 (0.69)	0 (0.00)
Metabolism and nutrition disorders	0 (0.00)	1 (0.70)
Neoplasms benign, malignant and unspecified	0 (0.00)	1 (0.70)
Social circumstances	1 (0.69)	0 (0.00)
Surgical and medical procedures	0 (0.00)	1 (0.70)

TABLE 4 Number of participants experiencing a related AE during the intervention phase, by treatment group

Related AE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	5 (4.45)	9 (6.29)
Injury, poisoning and procedural complications	1 (0.69)	1 (0.70)
Musculoskeletal and connective tissue disorders	4 (2.76)	3 (2.10)
General disorders and administration site condition	1 (0.69)	2 (1.40)
Nervous system disorders	0 (0.00)	2 (1.40)
Eye disorders	0 (0.00)	1 (0.70)
Metabolism and nutrition disorders	0 (0.00)	1 (0.70)

TABLE 5 Number of participants experiencing a SAE during the intervention phase, by treatment group

SAE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	17 (11.72)	11 (7.69)
Injury, poisoning and procedural complications	1 (0.69)	2 (1.40)
Infections and infestations	6 (4.14)	0 (0.00)
Musculoskeletal and connective tissue disorders	1 (0.69)	0 (0.00)
General disorders and administration site conditions	4 (2.76)	0 (0.00)
Nervous system disorders	4 (2.76)	2 (1.40)
Gastrointestinal disorders	1 (0.69)	0 (0.00)
Psychiatric disorders	1 (0.69)	1 (0.70)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	1 (0.70)
Cardiac disorders	1 (0.69)	3 (2.10)
Immune system disorders	1 (0.69)	0 (0.00)
Neoplasms benign, malignant and unspecified	0 (0.00)	1 (0.70)
Surgical and medical procedures	0 (0.00)	1 (0.70)

TABLE 6 Number of participants experiencing an unexpected SAE during the intervention phase, by treatment group

Unexpected SAE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	9 (6.21)	4 (2.80)
Injury, poisoning and procedural complications	0 (0.00)	1 (0.70)
Infections and infestations	4 (2.76)	0 (0.00)
General disorders and administration site condition	1 (0.69)	0 (0.00)
Nervous system disorders	2 (1.38)	0 (0.00)
Gastrointestinal disorders	1 (0.69)	0 (0.00)
Psychiatric disorders	0 (0.00)	1 (0.70)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	1 (0.70)
Cardiac disorders	0 (0.00)	1 (0.70)
Immune system disorders	1 (0.69)	0 (0.00)

TABLE 7 Number of participants experiencing an AE during the follow-up phase, by treatment group

AE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	22 (15.17)	35 (24.48)
Injury, poisoning and procedural complications	8 (5.52)	10 (6.99)
Infections and infestations	7 (4.83)	6 (4.20)
Skin and subcutaneous tissue disorders	1 (0.69)	4 (2.80)
General disorders and administration site conditions	2 (1.38)	5 (3.50)
Nervous system disorders	3 (2.07)	7 (4.90)
Gastrointestinal disorders	1 (0.69)	3 (2.10)
Vascular disorders	0 (0.00)	1 (0.70)
Psychiatric disorders	2 (1.38)	1 (0.70)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	3 (2.10)
Renal and urinary disorders	1 (0.69)	0 (0.00)
Eye disorders	0 (0.00)	1 (0.70)
Neoplasms benign, malignant and unspecified	0 (0.00)	1 (0.70)
Musculoskeletal and connective tissue disorders	1 (0.69)	1 (0.70)
Surgical and medical procedures	3 (2.07)	2 (1.40)

TABLE 8 Number of participants experiencing a related AE during the follow-up phase, by treatment group

Related AE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	3 (2.07)	0 (0.00)
Musculoskeletal and connective tissue disorders	1 (0.69)	0 (0.00)
General disorders and administration site condition	1 (0.69)	0 (0.00)
Nervous system disorders	1 (0.69)	0 (0.00)

TABLE 9 Number of participants experiencing a SAE during the follow-up phase, by treatment group

SAE	Treatment group, <i>n</i> (%)	
	FST + CPT (<i>N</i> = 145)	MPT + CPT (<i>N</i> = 143)
Any event	5 (3.45)	13 (9.09)
Injury, poisoning and procedural complications	1 (0.69)	2 (1.40)
General disorders and administration site conditions	1 (0.69)	1 (0.70)
Nervous system disorders	1 (0.69)	6 (4.20)
Gastrointestinal disorders	0 (0.00)	1 (0.70)
Psychiatric disorders	1 (0.69)	2 (1.40)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	2 (1.40)
Renal and urinary disorders	1 (0.69)	0 (0.00)
Neoplasms benign, malignant and unspecified	0 (0.00)	1 (0.70)
Surgical and medical procedures	1 (0.69)	0 (0.00)

TABLE 10 Number of participants experiencing an unexpected SAE during the follow-up phase, by treatment group

Unexpected SAE	Treatment group, n (%)	
	FST + CPT (N = 145)	MPT + CPT (N = 143)
Any event	2 (1.38)	7 (4.90)
Injury, poisoning and procedural complications	0 (0.00)	1 (0.70)
Nervous system disorders	0 (0.00)	2 (1.40)
Gastrointestinal disorders	0 (0.00)	1 (0.70)
Psychiatric disorders	0 (0.00)	2 (1.40)
Respiratory, thoracic and mediastinal disorders	0 (0.00)	2 (1.40)
Renal and urinary disorders	1 (0.69)	0 (0.00)
Neoplasms benign, malignant and unspecified	0 (0.00)	1 (0.70)
Surgical and medical procedures	1 (0.69)	0 (0.00)

Primary clinical efficacy analysis

The primary outcome measure was ARAT score. There were 126 participants for the FST + CPT group and 114 for the MPT + CPT group with data at both baseline and outcome (*Table 11*). At follow-up, the number of participants with data at baseline had reduced to 104 for the FST + CPT group and to 100 for the MPT + CPT group (*Table 12*). Both groups showed improvement (mean and SD) from baseline at outcome [FST + CPT = 9.70 (SD 11.72) and MPT + CPT = 7.90 (SD 9.18)], but there was little difference between the groups and this did not reach statistical significance ($p = 0.298$). Further improvements were evident at follow-up with mean (SD) changes from baseline of 11.10 (SD 14.68) for the FST + CPT group and 10.3 (SD 10.74) for the MPT + CPT group. Again, this difference was small and did not reach statistical significance ($p = 0.743$).

Secondary clinical efficacy analysis

Secondary clinical efficacy outcome measures (*Tables 13–18*) showed a similar pattern to the ARAT scores (primary outcome) in terms of their mean improvements. SDs indicated more variability in response for grip and pinch force. Differences between groups were small and did not reach statistical significance.

TABLE 11 Change from baseline to outcome for ARAT score, paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference and p -value of change between group
Change at outcome	FST + CPT	126	24.40 (18.45)	34.10 (17.81)	9.70 (11.72)	9.80 (7.87 to 11.73)	1.35 (-1.20 to 3.90); $p = 0.298$
	MPT + CPT	114	26.50 (17.78)	34.40 (18.68)	7.90 (9.18)	8.45 (6.41 to 10.49)	

a Number of participants with data at both baseline and outcome.

TABLE 12 Change from baseline to follow-up for ARAT score, paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Follow-up	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at follow-up	FST + CPT	104	25.80 (18.21)	36.80 (19.14)	11.10 (14.68)	10.90 (8.31 to 13.49)	0.55 (–2.77 to 3.88); <i>p</i> = 0.743
	MPT + CPT	100	27.10 (17.49)	37.40 (17.50)	10.3 (10.74)	10.35 (7.66 to 13.03)	

a Number of participants with data at both baseline and follow-up.

TABLE 13 Change from baseline to outcome for grip force (kg), paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at outcome	FST + CPT	122	7.60 (8.72)	10.7 (9.99)	3.1 (7.11)	3.98 (2.74 to 5.21)	0.47 (–1.16 to 2.09); <i>p</i> = 0.571
	MPT + CPT	115	7.20 (8.19)	9.90 (9.35)	2.70 (6.25)	3.51 (2.24 to 4.78)	

a Number of participants with data at both baseline and outcome.

TABLE 14 Change from baseline to follow-up for grip force (kg), paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Follow-up	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at follow-up	FST + CPT	101	7.40 (8.50)	11.80 (10.20)	4.4 (7.02)	5.33 (3.70 to 6.95)	–0.29 (–2.37 to 1.79); <i>p</i> = 0.785
	MPT + CPT	97	7.20 (8.35)	12.00 (10.10)	4.70 (8.71)	5.62 (3.95 to 7.28)	

a Number of participants with data at both baseline and follow-up.

TABLE 15 Change from baseline to outcome for pinch force (kg), paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at outcome	FST + CPT	115	2.20 (2.20)	3.00 (2.93)	0.90 (2.13)	0.91 (0.48 to 1.33)	0.02 (–0.54 to 0.59); <i>p</i> = 0.934
	MPT + CPT	109	2.00 (2.30)	2.90 (2.88)	0.90 (2.16)	0.89 (0.45 to 1.32)	

a Number of participants with data at both baseline and outcome.

TABLE 16 Change from baseline to follow-up for pinch force (kg), paretic upper limb for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Follow-up	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at follow-up	FST + CPT	94	2.30 (2.22)	3.30 (2.45)	1.00 (2.19)	1.16 (0.62 to 1.71)	-0.30 (-0.98 to 0.39); <i>p</i> = 0.395
	MPT + CPT	95	2.10 (2.24)	3.50 (3.09)	1.40 (2.76)	1.46 (0.92 to 2.01)	

^a Number of participants with data at both baseline and follow-up.

TABLE 17 Change from baseline to outcome for WMFT performance for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at outcome	FST + CPT	117	36.60 (19.97)	47.80 (19.70)	11.20 (10.62)	11.31 (0.35 to 13.27)	0.65 (-1.91 to 3.21); <i>p</i> = 0.616
	MPT + CPT	109	39.00 (16.84)	49.00 (18.52)	10.00 (9.61)	10.65 (8.62 to 12.69)	

^a Number of participants with data at both baseline and outcome.

TABLE 18 Change from baseline to follow-up for WMFT performance for participants with data at both time points

Comparison	Treatment group	Number of participants ^a	Mean (SD)			Mean (95% CI)	
			Baseline	Follow-up	Change	Least squares	Least squares difference and <i>p</i> -value of change between group
Change at follow-up	FST + CPT	98	38.30 (19.42)	51.80 (19.83)	13.50 (14.28)	14.21 (11.53 to 16.88)	0.01 (-3.46 to 3.47); <i>p</i> = 0.997
	MPT + CPT	93	39.30 (16.96)	52.60 (18.41)	13.30 (11.55)	14.20 (11.40 to 17.00)	

^a Number of participants with data at both baseline and follow-up.

Chapter 4 Results: neural correlates of clinical improvement

Objective addressed

To identify the similarities and differences in the neural correlates of clinical improvement in upper limb motor function in response to (1) FST + CPT and (2) MPT + CPT. To reiterate, baseline measures were made immediately before randomisation and outcome measures made at the end of the 6-week intervention phase (see *Chapter 2, Design*).

Flow of participants through the correlates analysis

Magnetic resonance imaging

Structural MR scans were undertaken for those participants who had no contraindications, had provided separate informed consent for this part of the assessment and who could travel to the neuroimaging facility. MR scans were undertaken for 94 (32.6%) participants at baseline and 62 (25.3%) participants at outcome. Reasons for non-completion of MRI are shown in *Table 19*.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was undertaken by those participants who had no contraindications. The TMS measures were made with 111 (38.5%) participants at baseline and 83 (33.9%) at outcome. Reasons for no TMS are shown in *Table 20*.

Neural variables at baseline and outcome

The numbers of participants for whom neuroimaging variables were available at outcome and follow-up are shown in *Tables 21–23*. The number of participants varies from 45 for corticocortical and corticospinal anatomical connectivity at outcome (see *Table 21*) to 84 for volume of the stroke lesion at baseline (see *Table 23*).

TABLE 19 The MRI (neuroimaging) data acquisition at baseline and outcome

Data	Time point, <i>n</i> (%)	
	Baseline (<i>N</i> = 288) ^a	Outcome (<i>N</i> = 245) ^{a,b}
MRI data acquired		
Attended for neuroimaging	94 (32.6)	62 (25.3)
Reason for lack of data		
Unable to attend	31 (10.8)	39 (15.9)
Did not consent	44 (15.3)	62 (25.3)
Other	119 (41.3)	106 (43.3)

^a Data obtained from clinical trial unit locked (raw) database.

^b Clinical trial unit data account for 269 participants in terms of attendance and non-attendance for MRI scanning.

TABLE 20 TMS data acquisition at baseline and outcome

Data	Time point, <i>n</i> (%)	
	Baseline (<i>N</i> = 288) ^a	Outcome (<i>N</i> = 245) ^{a,b}
TMS data acquired		
Attended for TMS	111 (38.5)	83 (33.9)
Reason for lack of data		
Did not consent for TMS	30 (10.4)	39 (15.9)
Unable to attend	21 (7.3)	39 (15.9)
Other	126 (43.8)	114 (46.5)

a Data obtained from clinical trial unit locked (raw) database.

b Clinical trial unit data account for 275 participants in terms of attendance and non-attendance for TMS.

TABLE 21 Corticocortical anatomical connectivity (FA MNI corpus callosum midline, range 0–1) at baseline and outcome

Statistic	Time point					
	Baseline			Outcome		
	FST + CPT	MPT + CPT	All	FST + CPT	MPT + CPT	All
Number of participants	42	38	80	25	20	45
Mean	0.4	0.4	0.4	0.4	0.4	0.4
SD	0.09	0.08	0.08	0.09	0.08	0.08
Median	0.4	0.4	0.4	0.4	0.5	0.4
Minimum–maximum	0.21–0.54	0.29–0.55	0.21–0.55	0.22–0.54	0.31–0.57	0.22–0.57
IQR	0.342–0.47	0.34–0.49	0.34–0.47	0.35–0.46	0.35–0.49	0.35–0.47

IQR, interquartile range.

Final report from clinical trial unit reported to only one decimal place; however, any differences between groups would be expected to be < 0.1 so it would be better to report two decimal places.

TABLE 22 Corticospinal anatomical connectivity (asymmetry FA CST, range –1 to 1) at baseline and outcome

Statistic	Time point					
	Baseline			Outcome		
	FST + CPT	MPT + CPT	All	FST + CPT	MPT + CPT	All
Number of participants	42	38	80	25	20	45
Mean	0.0	0.0	0.0	0.0	0.0	0.0
SD	0.04	0.05	0.05	0.05	0.05	0.05
Median	0.0	0.0	0.0	0.0	0.0	0.0
Minimum–maximum	–0.06 to 0.14	–0.07 to 0.15	–0.07 to 0.15	–0.02 to 0.18	–0.04 to 0.18	–0.04 to 0.18
IQR	0.01 to 0.06	–0.02 to 0.06	0.001 to 0.06	0.00 to 0.07	–0.01 to 0.06	–0.01 to 0.07

IQR, interquartile range.

Final report from clinical trial unit reported to only one decimal place; however, any differences between groups would be expected to be < 0.1 so it would be better to report two decimal places.

TABLE 23 Volume of the stroke lesion (mm³) at baseline and outcome

Statistic	Time point					
	Baseline			Outcome		
	FST + CPT	MPT + CPT	All	FST + CPT	MPT + CPT	All
Number of participants	44	40	84	29	23	52
Mean	23,847.89	25,476.38	24,623.36	28,129.97	32,398.22	30,017.85
SD	47,664.63	59,957.23	53,542.90	60,884.91	57,371.06	58,818.52
Median	6537.50	2486.00	4293.00	1753.00	2139.00	1946.00
Minimum–maximum	91.00–218,162.00	56.00–324,152.00	56.00–324,152.00	99.00–252,757.00	54.00–221,613.00	54.00–252,757.00
IQR	1067.50–19,551.50	474.00–14,046.50	845.50–17,160.50	919.00–13,945.00	788.00–45,496.00	822.00–28,184.50
IQR, interquartile range.						

Change in neural variables derived from neuroimaging between baseline and outcome for those participants with data at both visits and ARAT score data at both visits is shown in *Table 24*. There were no statistically significant differences between the two groups for change in any of these variables.

The number of participants for whom neural variables derived from TMS were available at outcome and follow-up together are shown in *Tables 25* and *26*. The number of participants ranges between 72 for RMT for paretic extensor carpi radialis (pECR) at outcome (see *Table 26*) and 110 for presence of a MEP of pBB and pECR at baseline (see *Table 25*).

Change between baseline and outcome for RMT for pBB and pECR muscles for those participants with data at both visits and ARAT score data at both visits is shown in *Table 27*. There are no statistically significant differences between the two groups for change in either of these variables.

TABLE 24 Change (outcome – baseline) in MRI variables for participants with data at both visits

Variable	Group	n	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; p-value
Lesion volume (mm ³)	FST + CPT	24	8.20 (2.13)	8.10 (2.17)	-0.10 (0.45)	-0.11 (-0.31 to 0.09)	-0.12 (-0.36 to 0.13); p = 0.349
	MPT + CPT	20	8.20 (2.49)	8.10 (2.40)	-0.00 (0.32)	0.01 (-0.21 to 0.22)	
Corticocortical connectivity ^a	FST + CPT	20	0.38 (0.09)	0.38 (0.09)	-0.00 (0.02)	-0.01 (-0.02 to 0.01)	0.01 (-0.01 to 0.03); p = 0.386
	MPT + CPT	18	0.45 (0.07)	0.43 (0.08)	-0.01 (0.03)	-0.02 (-0.03 to 0.00)	
Corticospinal connectivity ^b	FST + CPT	20	0.03 (0.05)	0.03 (0.04)	0.00 (0.01)	0.00 (-0.01 to 0.02)	-0.01 (-0.02 to 0.01); p = 0.524
	MPT + CPT	18	0.01 (0.05)	0.031 (0.05)	0.02 (0.04)	0.01 (-0.01 to 0.03)	

a FA MNI corpus callosum.
b Asymmetry ipsilesional : contralesional MNI CSTS.

TABLE 25 Presence of a MEP for pBB and pECR at baseline and outcome

MEP	Time point					
	Baseline			Outcome		
	FST + CPT	MPT + CPT	All	FST + CPT	MPT + CPT	All
pBB						
Number	53	57	110	43	39	82
Yes, n (%)	37 (69.81)	43 (75.44)	80 (72.73)	39 (90.70)	34 (87.18)	73 (89.02)
No, n (%)	16 (30.19)	14 (24.56)	30 (27.27)	4 (9.30)	5 (12.82)	9 (10.98)
pECR						
Number	53	57	110	42	39	81
Yes, n (%)	39 (73.58)	45 (78.95)	84 (76.36)	37 (88.10)	35 (89.74)	72 (88.89)
No, n (%)	14 (26.42)	12 (21.05)	26 (23.64)	5 (11.90)	4 (10.26)	9 (11.11)

TABLE 26 Resting motor threshold (% of stimulator output) when MEP present in pBB (RMT pBB) and pECR (RMT pECR) at baseline and outcome

MEP	Time point					
	Baseline			Outcome		
	FST + CPT	MPT + CPT	All	FST + CPT	MPT + CPT	All
pBB						
Number	37	43	80	39	34	73
Mean	61.1	63.0	62.1	65.9	69.9	67.8
SD	11.49	14.39	13.08	18.12	16.59	17.42
Median	60.0	66.0	60.0	63.0	71.5	65.0
Minimum–maximum	38–98	27–85	27–98	34–96	39–98	34–98
IQR	54–66	53–74	54–70	51–76	55–85	55–85
pECR						
Number	39	44	83	37	35	72
Mean	52.4	54.5	53.5	57.4	57.9	57.6
SD	12.30	15.27	13.91	18.58	16.40	17.43
Median	50.0	52.5	51.0	55.0	53.0	54.0
Minimum–maximum	24–90	27–94	24–94	27–95	33–95	27–95
IQR	46–58	44–61	45–60	47–63	44–70	44–68
IQR, interquartile range.						

TABLE 27 Change (outcome – baseline) in RMT for pBB and pECR for participants with data at both visits

Variable	Group	n	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; p-value
pBB	FST + CPT	28	61.6 (12.07)	60.6 (13.61)	–1.0 (14.27)	–0.82 (–6.32 to 4.68)	–2.87 (–8.91 to 3.16); p = 0.343
	MPT + CPT	27	62.5 (13.83)	65.0 (14.90)	2.5 (10.06)	2.06 (–3.86 to 7.97)	
pECR	FST + CPT	28	53.1 (13.15)	52.0 (11.62)	–1.1 (11.46)	–3.29 (–7.68 to 1.09)	0.98 (–4.31 to 6.28); p = 0.710
	MPT + CPT	27	57.4 (17.16)	53.2 (12.93)	–4.2 (12.98)	–4.28 (–9.19 to 0.63)	

The correlations between change, from baseline to outcome, between neural variables and ARAT score ranged from $r = -0.147$ ($p = 0.385$) for all participants' corticospinal connectivity to $r = 0.199$ ($p = 0.320$) for the MPT + CPT group for RMT pBB (Table 28). Consequently, the neural correlates of improvement in ARAT score were similar for the two groups.

TABLE 28 Correlations between change (from baseline to outcome) in neural correlates and paretic ARAT total score (primary outcome measure)

Neural variable	Treatment group								
	FST + CPT			MPT + CPT			All		
	Number of participants	r-value	p-value	Number of participants	r-value	p-value	Number of participants	r-value	p-value
Volume of the stroke lesion	24	−0.021	0.921	19	−0.043	0.863	43	−0.042	0.787
Corticocortical anatomical connectivity	20	0.092	0.699	17	−0.029	0.913	37	0.069	0.684
Corticospinal anatomical connectivity	20	−0.031	0.897	17	−0.306	0.232	37	−0.147	0.385
RMT – pBB	28	0.095	0.631	27	0.199	0.320	55	0.093	0.501
RMT – pECR	28	−0.080	0.635	27	0.043	0.831	55	−0.001	0.996

Chapter 5 Results: predictive markers of clinical improvement

Objective addressed

To determine if any pretreatment parameters or any combination of pretreatment parameters [(a) anatomical location of infarction, (b) volume of the stroke lesion, (c) residual structural corticocortical connectivity, (d) residual corticospinal connectivity and (e) brain–muscle functional connectivity (derived from TMS)] are sufficiently predictive of upper limb recovery after stroke to enable physical therapy to be targeted at those people most likely to respond.

Participants with neural variables data at baseline

Data on the number of participants at baseline and the values of the neural variables are presented in *Tables 21–28*.

Change at outcome from baseline for Action Research Arm Test score

For those people with both ARAT score and neural variable data at baseline and outcome there were no statistically significant interaction effects (*Table 29*). The data for change in ARAT score underlying these interaction effects are provided in *Tables 30–34*. There are no statistically significant differences between the subgroups for any of the baseline characteristics.

TABLE 29 Subgroup analysis of interaction effect between baseline neural variables and change in paretic ARAT total score from baseline to outcome

Baseline characteristic	Interaction <i>p</i> -value
Anatomical location of stroke lesion: MNI CST affected	0.384
Volume of the stroke lesion (logged)	0.762
Corticocortical anatomical connectivity (FA MNI corpus callosum midline)	0.723
Corticocortical anatomical connectivity (asymmetry ipsilesional : contralesional MNI CSTS)	0.553
Presence of MEP pBB	0.237
pBB RMT	0.697
Presence of MEP pECR	0.193
pECR RMT	0.503

TABLE 30 Change (outcome – baseline) in paretic ARAT total score for participants with data at both visits and measure of corticocortico anatomical connectivity

Variable	Group	Number of participants	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; <i>p</i> -value
Corticocortical connectivity value below median	FST + CPT	18	27.4 (20.29)	35.6 (17.54)	8.2 (9.47)	11.92 (6.74 to 17.10)	3.83 (–2.41 to 10.07); <i>p</i> = 0.218
	MPT + CPT	14	27.4 (17.53)	34.0 (20.04)	6.6 (6.87)	8.09 (3.12 to 13.06)	
Corticocortical connectivity value equal to or above median	FST + CPT	18	22.3 (18.22)	39.3 (14.58)	17.1 (13.45)	16.95 (11.22 to 22.68)	4.29 (–2.99 to 11.58); <i>p</i> = 0.238
	MPT + CPT	18	24.6 (17.74)	33.8 (19.65)	9.2 (6.78)	12.66 (5.40 to 19.92)	

TABLE 31 Change (outcome – baseline) in paretic ARAT total score for participants with data at both visits and measure of stroke lesion volume

Variable	Group	Number of participants	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; <i>p</i> -value
Lesion volume value below median	FST + CPT	17	25.1 (18.64)	41.2 (14.91)	16.1 (11.99)	16.05 (10.71 to 21.38)	5.3 (–1.09 to 11.70) <i>p</i> = 0.101
	MPT + CPT	20	28.7 (18.96)	38.3 (18.26)	9.7 (8.03)	10.74 (5.62 to 15.87)	
Lesion volume value equal to or above median	FST + CPT	21	22.8 (19.99)	32.5 (17.44)	9.8 (12.36)	12.59 (6.22 to 18.96)	4.44 (–2.89 to 11.76) <i>p</i> = 0.225
	MPT + CPT	14	22.4 (16.98)	27.7 (19.57)	5.4 (5.39)	8.15 (0.02 to 16.29)	

TABLE 32 Change (outcome – baseline) in paretic ARAT total score for participants with data at both visits and measure of anatomical overlap of the stroke lesion with the CST

Variable	Group	Number of participants	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; <i>p</i> -value
CST lesioned = yes	FST + CPT	33	23.3 (19.67)	35.2 (17.35)	11.9 (12.32)	13.9 (9.55 to 18.29)	2.88 (–2.29 to 8.04); <i>p</i> = 0.269
	MPT + CPT	27	25.7 (17.04)	34.0 (18.77)	8.30 (7.40)	11.0 (6.48 to 15.60)	
CST lesioned = no	FST + CPT	5	27.0 (17.07)	44.2 (9.42)	17.2 (13.65)	26.1 (–9.59 to 61.82)	20.64 (–14.07 to 55.36); <i>p</i> = 0.187
	MPT + CPT	7	27.6 (23.59)	33.7 (22.63)	6.1 (7.13)	5.5 (–12.28 to 23.22)	

TABLE 33 Change (outcome – baseline) in paretic ARAT total score for participants with data at both visits and measure of asymmetry of the ipsilesional and contralesional CST connectivity

Variable	Group	Number of participants	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; <i>p</i> -value
Ratio value below median	FST + CPT	19	28.6 (16.69)	43.2 (11.54)	14.6 (11.90)	14.90 (8.84 to 20.96)	2.42 (–3.95 to 8.79) <i>p</i> = 0.443
	MPT + CPT	16	31.9 (15.80)	42.4 (16.15)	10.4 (6.65)	12.48 (6.55 to 18.42)	
Ratio value equal to or above median	FST + CPT	17	20.6 (21.36)	31.1 (18.11)	10.4 (12.73)	15.38 (7.81 to 22.95)	6.62 (–0.33 to 13.56) <i>p</i> = 0.061
	MPT + CPT	16	19.7 (17.26)	25.4 (19.26)	5.7 (6.35)	8.76 (1.51 to 16.02)	

TABLE 34 Change (outcome – baseline) in paretic ARAT total score for participants with data at both visits and measure of MEP in pBB and pECR

Variable	Group	Number of participants	Mean (SD)			Mean (95% CI)	
			Baseline	Outcome	Change	Least squares	Least squares difference; <i>p</i> -value
MEP pBB = yes	FST + CPT	34	32.2 (16.69)	43.0 (12.76)	10.9 (11.85)	11.68 (8.24 to 15.12)	3.19 (–0.71 to 7.09); <i>p</i> = 0.107
	MPT + CPT	36	34.0 (15.05)	40.3 (14.34)	6.2 (7.95)	8.49 (5.04 to 11.93)	
MEP pBB = no	FST + CPT	16	12.6 (15.34)	22.1 (21.30)	9.4 (11.43)	11.62 (3.68 to 19.56)	–0.60 (–7.38 to 6.18); <i>p</i> = 0.856
	MPT + CPT	13	12.7 (13.31)	22.2 (16.60)	9.5 (7.41)	12.22 (3.07 to 21.37)	
MEP pECR = yes	FST + CPT	36	31.9 (16.87)	43.6 (12.87)	11.7 (12.37)	12.67 (9.31 to 16.03)	3.41 (–0.53 to 7.34); <i>p</i> = 0.089
	MPT + CPT	38	33.8 (14.60)	40.6 (13.43)	6.8 (7.52)	9.26 (5.89 to 12.64)	
MEP pECR = no	FST + CPT	14	10.4 (13.15)	17.5 (18.15)	7.1 (8.98)	14.97 (–2.04 to 31.98)	–1.74 (–9.54 to 6.07); <i>p</i> = 0.646
	MPT + CPT	11	9.7 (12.62)	17.8 (15.87)	8.1 (9.31)	16.71 (–1.18 to 34.60)	

Chapter 6 Discussion

The present trial combined investigation of the clinical efficacy of MPT and FST together with (1) identification of the neural correlates of response to therapy as a basis for identifying precise therapy target(s) and (2) understanding whether or not neural characteristics at baseline could indicate response to MPT and FST and thereby identify which stroke survivors should receive which of these therapies. Hence, investigating efficacy and mechanisms together in the present trial provides robust information for subsequent definitive trials to investigate the effectiveness of MPT and FST targeted at the underlying central nervous system mechanisms of their means of action in those people most likely to respond. The need for such research has been highlighted by the UK Academy of Medical Sciences,⁵⁵ the US National Institutes of Health¹⁶ and an international consensus group.¹⁵

Summary of main results

Clinical efficacy: summary of main results

This study found little difference between the groups in upper limb recovery in response to the two forms of physical therapy. Differences did not reach statistical significance. Importantly, the variability in response within groups was considerable, especially for (hand) grip force and (finger) pinch force.

Neural correlates of clinical improvement: summary of main results

This study found no clinically important association between clinical improvement and change in the neural measures in response to either trial intervention. However, the sample sizes available for analysis of neural therapy interactions were small. Therefore, there was little chance of detecting any significant probability.

Predictive markers of clinical improvement: summary of main results

This study found no interaction effects between baseline neural variables and change in ARAT total score (primary outcome measure) for the paretic upper limb between baseline and outcome (primary time point). As for the neural correlates of clinical improvement analysis, the sample sizes available for analysis of neural therapy interactions were small, which gave little chance of detecting significant probability.

Strengths and limitations

Bias protection for this trial was provided by the blinding of assessors to group allocation, concealment of randomisation order, group allocation via independent telephone randomisation service, adhering to the intention-to-treat principle and reporting all planned outcomes. This trial evaluated a behavioural intervention and, therefore, it was not possible to blind research therapists, participants or clinical staff to the allocated intervention. Although this is perceived as a distinct limitation in drug trials, it is recognised that double blinding is not possible in trials of many stroke rehabilitation interventions. Because of staffing challenges in centres at some points in the trial, it was not always possible to have blinded assessment of the behavioural outcomes.

The sample size for this trial was estimated by a power calculation informed by data from our early-phase trial.²⁸ The estimated sample size allowed for an attrition rate of 10% at the primary end point of outcome. In the event our attrition rate at outcome was 12.5%, which is substantially lower than the 25% reported by the well-regarded EXCITE (Extremity Constraint-Induced Therapy Evaluation) trial of CIMT.⁵⁶

This trial was congruent with the requirements for stroke rehabilitation trials.⁴⁰ A strength for all aspects of this trial is that the interventions, both MPT and FST, were described in sufficient detail to enable both research replication of the trial and transferability of results to clinical practice.^{48,57,58} Thus, this trial has followed the recommendations for improving rehabilitation research.^{57,59}

The experimental FST + CPT in this trial was consistent with key principles of neural plasticity^{9,60} and was therefore well placed to (1) exhibit clinical efficacy and (2) form a useful probe of correlates of, and indicators for, upper limb recovery.

Clinical efficacy: strengths and limitations

An important strength of the trial reported here is that 59% of participants were recruited within 30 days of stroke. Early rehabilitation is recommended because the brain has most potential for reorganisation particularly in the first month after stroke but also in the following 2 months.⁹ In clinical practice, most rehabilitation is provided in this early period and yet most rehabilitation trials are conducted later in recovery. A recent systematic review found that only 5.6% of identified RCTs met a required quality threshold and were conducted within the first month after stroke.⁶¹ Therefore, the present trial is likely to be important for stroke rehabilitation research and practice.

Another strength of the trial is that the sample did not just include stroke survivors with mild paresis after stroke who were therefore expected to make a good recovery. The participants in this trial are representative of those who receive upper limb rehabilitation in clinical stroke services. The results are therefore directly relevant to clinical practice.

The power calculation that informed the sample size for this trial accounted for the clustering of participants within therapists. In the event, staff turnover and securing of additional resource in the form of additional therapists meant that many more therapists than anticipated initially provided either MPT or FST to participants in this trial. Although this is a limitation in terms of not allowing for the clustering analysis, it is also a strength as a greater number of therapists indicates higher generalisability to the clinical environment.

Neural correlates of clinical improvement: strengths and limitations

A key strength of this mechanistic study is that it was embedded within a robust clinical trial. Thus, unlike many mechanistic studies, the one reported here guarded against potential risk of bias and allowed for sufficient description of the interventions provided. Although the number of participants in this mechanistic study was lower than anticipated, it still recruited many more participants than many such studies.

This analysis was restricted by the low proportion of participants who had both (1) full sets of clinical data and (2) neural measures at the key time points of baseline and outcome. This ranged from 37 participants for corticocortical anatomical connectivity to 55 participants for RMT in pBB and pECR muscles.

Predictive markers of clinical improvement: strengths and limitations

Again, as for the neural correlates study, being embedded in a RCT provides strength to this mechanistic study. However, it was disappointing that a greater number of participants were unable to be included in the analysis. On the other hand, we have shown that it is possible to conduct mechanistic neural studies in pragmatic clinical trials. Furthermore, we have shown that these highly specialised neural measures can be made in clinical settings that are not associated with specialist neurological centres and have not previously conducted these mechanistic investigations. However, the challenges to this approach are evident in the number of measures not undertaken for 'other' reasons (see *Tables 19 and 20*).

Relationship to previous studies

Progress in stroke rehabilitation has been hampered by a paucity of large-scale projects in which neuroscientists and clinicians have been able to work together and so inform each other's approach to a single clinical problem, such as the treatment of upper limb weakness.⁵⁵ For this trial, we combined neuroscience and clinical science expertise in the largest study of its kind to investigate underlying mechanisms of motor recovery in a representative sample of patients early after stroke with substantial to moderate upper limb motor impairment using well-characterised physical therapies.

Clinical efficacy: relationship to previous studies

The results of the trial reported here build on early-phase findings that suggest a trend towards better upper limb recovery, as assessed by ARAT score, in response to FST + CPT compared with MPT + CPT early after stroke.²⁸ However, the findings of the present trial, with a larger sample size, showed no difference between FST + CPT and MPT + CPT in respect of improvement of ARAT score over the 6-week intervention phase.

That MPT + CPT was found to produce equivalent benefit to FST + CPT is interesting, as FST is based on the findings that task-specific training drives recovery after stroke⁷ and that the largest impact on upper limb improvement is loss of muscle strength.^{18,19} In contrast, MPT concentrates on enhancing the quality of movement during whole or part functional tasks and not on repetitive progressive training of those everyday tasks. Although there is some evidence of effect of such impairment-based therapy,³⁸ a meta-analysis found that conceptually different physical therapies have equal efficacy.³⁹

Noticeable from these results is that there is substantial variation around the mean change from baseline for both FST + CPT and MPT + CPT (see *Tables 11–18*). Therefore, the present findings support the concept underlying the scientific driver for this trial, namely that stroke survivors respond differently to different physical therapies.¹⁹

Neural correlates of clinical improvement: relationship to previous studies

Published studies report that there are different neural changes for physical therapies found to have more benefit than the comparator intervention.^{60,62–64} However, the trial reported here found that the mean changes of ARAT score (primary outcome) in response to both interventions were above the clinical important difference of six points (see *Table 11*), although there was not a statistically significant difference between the groups, and there were no differences between the groups for the potential mechanisms of recovery of corticocortical connectivity, corticospinal connectivity or RMT of corticospinal functional connectivity for both muscles of interest (see *Tables 24* and *27*). Earlier studies have been smaller in scale (e.g. $n = 13$,⁶² $n = 12$,⁶⁰ $n = 14$ ⁶³ and $n = 23$ ⁶⁴) than the present trial, but the trial reported here had larger sample sizes for the MRI variable ($n = 38$) and the TMS variables ($n = 55$). Another important difference to the present trial is that earlier studies show a potential risk of bias in the method of randomisation^{60,62,63} and the use of blinded assessors^{60,62} and selective recruitment,^{60,63} and one study was a post hoc analysis of a single-centre RCT.⁶⁴

Predictive markers of clinical improvement: relationship to previous studies

Although identification of clinical prediction rules for physical therapy interventions is a research priority in physical rehabilitation, a systematic review identified only six RCTs.⁶⁵ None of the identified publications was concerned with stroke rehabilitation.⁶⁵ It follows that the trial reported here is most likely one of the first trials designed to identify predictive markers of response to specific physical therapies early after stroke. Other investigations have been reported but are limited for use with people early after stroke because of lack of a comparator group, lack of specification of the therapy and/or lack of participants in the chronic phase after stroke.^{24,66,67}

Generalisability

The generalisability of this trial is considered in the wide inclusion criteria with direct relevance to clinical practice and the conduct of the trial in three different clinical centres.

Chapter 7 Conclusions

Objective 1

The trial reported here found small differences in the clinical efficacy of upper limb recovery between FST + CPT and MPT + CPT, but these did not reach statistical significance. Both groups showed increases in ARAT score (primary outcome measure) above the clinically important change. However, variation around the mean change from baseline scores was substantial in both groups.

Objective 2

The neural correlates of change were similar for the two forms of physical therapy. There were no statistically significant correlations between change in the neural correlates and change in clinical efficacy measures.

Objective 3

The trial reported here found that none of the pretreatment neural characteristics of interest predicted response to either FST + CPT or MPT + CPT.

Implications for health care

The findings of the trial reported here confirm clinical impressions and emerging research evidence of variation in response to specific therapies among people early after stroke.

Research recommendations

There is still an urgent need for evidence to guide decisions about (1) appropriate prescription of physical therapy for individuals and (2) the recovery mechanisms at which physical therapy should be targeted.

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Grant co-applicants

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Research colleagues

- Andrew Walker, formerly School of Health Sciences, UEA. Trial manager who set up the trial and oversaw the initial data collection stage.
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Clinical research colleagues

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Contributions of authors

Valerie M Pomeroy (Professor of Neurorehabilitation, UEA) was the chief investigator and was the principal investigator at the UEA, Norfolk Community Health and Care, and Norfolk and Norwich University Hospitals NHS Foundation Trust. She undertook the overall design of the study, supervised trial conduct, supervised conduct of trial in Norfolk, contributed to recruitment, wrote drafts and undertook the final editing of the report.

Susan M Hunter (Senior Lecturer, Institute for Applied Clinical Sciences, School of Health and Rehabilitation, Keele University) was the principal investigator at Keele University and NHS Staffordshire and Stoke-on-Trent Partnership Trust. She supported design of the study, provided training in intervention delivery to research therapists across all sites, supervised the conduct of the trial in North Staffordshire, contributed to recruitment of participants, provided intervention in the (long-term) absence of research therapists, conducted baseline and blinded outcome assessments in the (long-term) absence of research assessors, collected TMS data locally, contributed to the report and agreed the final version.

Heidi Johansen-Berg (Professor of Cognitive Neuroscience, University of Oxford) contributed to the overall study design, jointly supervised design conduct and analysis of neuroimaging aspects of the study, contributed to the report and agreed the final version.

Nick S Ward (Professor of Clinical Neurology and Neurorehabilitation, University College London Institute of Neurology) led neuroimaging aspects of the production of the protocol and conduct of the trial, contributed to the report and agreed the final version of the report.

Niamh Kennedy (Lecturer in Rehabilitation Neuroscience, UEA) led neurophysiological aspects of the production of the protocol and conduct of the trial, contributed to the report and agreed the final version of the report.

Elizabeth Chandler (Research Therapist, UEA) contributed to all trial operating procedures and development of CRFs, managed day-to-day conduct of the trial in Norfolk, produced recruitment data during the interim period between full-time trial managers, contributed to recruitment and provided experimental intervention, contributed to the report and agreed the final version of the report.

Christopher J Weir (Professor of Medical Statistics and Clinical Trials, University of Edinburgh) contributed to the design of the study, advised on the SAP, commented on drafts of the report and agreed the final copy version of the report.

John Rothwell (Professor of Human Neurophysiology, University College London Institute of Neurology) contributed to neurophysiological aspects of the protocol and oversaw the quality of data collection contributed to the report and agreed the final version of the report.

Alan Wing (Professor of Human Movement, School of Psychology, University of Birmingham) contributed to the production of the protocol, oversaw one of the clinical centres, contributed to the report and agreed the final version of the report.

Michael Grey (formerly Reader in Motor Neuroscience, University of Birmingham; currently Reader in Rehabilitation Neuroscience, UEA) led the conduct of neurophysiological measures in a key centre for this trial and is leading aspects of the analysis, contributed to the report and agreed final version of the report.

Garry Barton (Professor of Health Economics, UEA) led all aspects of the health economics investigation embedded in this trial, contributed to the report and agreed the final version of the report.

Nick Leavey (Clinical Trial Manager, UEA) managed the conduct of the trial across the three recruiting centres, contributed to the report and agreed the final copy version of the report.

Publications

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Pomeroy VM, Ward NS, Johansen-Berg H, van Vliet P, Burridge J, Hunter SM, *et al.* FAST INdiCATE Trial protocol. Clinical efficacy of functional strength training for upper limb motor recovery early after stroke: neural correlates and prognostic indicators. *Int J Stroke* 2014;**9**:240–5.

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Data sharing statement

All available data can be obtained by contacting the corresponding author.

Patient Data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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Appendix 1 The conventional physical therapy, therapy as usual, intervention

1. To reduce pain	<input type="checkbox"/>	3. To improve muscle activity/function	<input type="checkbox"/>	5. To improve gross mobility	<input type="checkbox"/>
2. To improve sensory awareness	<input type="checkbox"/>	4. To improve postural control	<input type="checkbox"/>	6. To improve endurance	<input type="checkbox"/>

Gross position of patient during activities used

1. Supine lying	<input type="checkbox"/>	4. non-paretic side lying	<input type="checkbox"/>	7. 4 pt kneeling	<input type="checkbox"/>	10. Standing	<input type="checkbox"/>
2. Crook lying	<input type="checkbox"/>	5. Sitting - 90°	<input type="checkbox"/>	8. 2 pt kneeling	<input type="checkbox"/>	11. Walking	<input type="checkbox"/>
3. Paretic side lying	<input type="checkbox"/>	6. Sitting – perch	<input type="checkbox"/>	9. ½ kneeling	<input type="checkbox"/>	12. Other	<input type="checkbox"/>

Equipment used

1. High hold/surface	<input type="checkbox"/>	4. Perching stool	<input type="checkbox"/>	7. Walking aid	<input type="checkbox"/>	10. Other	<input type="checkbox"/>
2. Low hold/surface	<input type="checkbox"/>	5. Rolled up towel	<input type="checkbox"/>	8. Tilt table	<input type="checkbox"/>		<input type="checkbox"/>
3. Hip high hold/surface	<input type="checkbox"/>	6. Gym ball	<input type="checkbox"/>	9. Standing frame			

Specific Physical Therapy interventions

1. Soft tissue mobilisation

1.1 Specific soft tissue mobilisation	<input type="checkbox"/>
1.2 Passive movement	<input type="checkbox"/>
1.3 Muscle stretching	<input type="checkbox"/>

2. Facilitation of activity in specific muscles

2.1 Imagery of specific muscle activity	<input type="checkbox"/>
2.2 Specific muscle activation	<input type="checkbox"/>
2.3 Activation of muscle activity during function	<input type="checkbox"/>

3. Facilitation of isolated (selective) joint movement

3.1 Imagery specific joint movement	<input type="checkbox"/>
3.2 Active assisted isolated joint movement	<input type="checkbox"/>
3.3 Facilitate specific joint movement during function	<input type="checkbox"/>

4. Facilitation of co-ordinated (combined) movement

4.1 Imagery of co-ordinated patterns of movement	<input type="checkbox"/>
4.2 Active assisted co-ordinated patterns of movement	<input type="checkbox"/>
4.3 Facilitate co-ordinated movement during function	<input type="checkbox"/>
4.4 Facilitate leg/foot activity from another body part	<input type="checkbox"/>

5. Resistive exercise

5.1 Resistance from therapist	<input type="checkbox"/>
5.2 Resistance from patient's bodyweight	<input type="checkbox"/>
5.3 Resistance from equipment	<input type="checkbox"/>

6. Specific sensory (tactile & proprioceptive) input

6.1 "Hands-on" techniques	<input type="checkbox"/>
6.2 Provision of environmental surface	<input type="checkbox"/>

7. Splinting techniques

7.1 Strapping	<input type="checkbox"/>
7.2 Splinting	<input type="checkbox"/>

8. Function – in lying towards sitting

8.1 PT "hands-on" techniques to re-ed posture	<input type="checkbox"/>
8.2 Re-ed of funct act through specific mvmt patterns	<input type="checkbox"/>
8.3 Rolling – functional activity training	<input type="checkbox"/>
8.4 Bridging - functional activity training	<input type="checkbox"/>
8.5 Lying to sitting – functional activity training	<input type="checkbox"/>
8.6 Sitting to lying - functional activity training	<input type="checkbox"/>
8.7 Static sitting balance training	<input type="checkbox"/>

9. Function – In sitting towards standing

9.1 PT "hands-on" techniques to re-ed posture	<input type="checkbox"/>
9.2 Re-ed of funct act through specific mvmt patterns	<input type="checkbox"/>
9.3 Dynamic sitting balance training	<input type="checkbox"/>
9.4 Transfers training	<input type="checkbox"/>
9.5 Sit to standing – functional activity training	<input type="checkbox"/>
9.6 Stand to sit – functional activity training	<input type="checkbox"/>

10. Function – In standing towards walking

10.1 PT "hands-on" techniques to re-ed posture	<input type="checkbox"/>
10.2 Re-ed of funct act through specific mvmt patterns	<input type="checkbox"/>
10.3 Static standing balance training	<input type="checkbox"/>
10.4 Dynamic standing balance training	<input type="checkbox"/>
10.5 One leg stand activities – functional training	<input type="checkbox"/>

11. Function – Walking and onwards

11.1 PT "hands-on" techniques to re-ed posture	<input type="checkbox"/>
11.2 Re-ed of funct act through specific mvmt patterns	<input type="checkbox"/>
11.3 Overground indoor walking training	<input type="checkbox"/>
11.4 Overground outdoor walking training	<input type="checkbox"/>
11.5 Treadmill walking/bicycle training	<input type="checkbox"/>
11.6 Obstacle negotiation training	<input type="checkbox"/>
11.7 Ascending/descending stair training	<input type="checkbox"/>

Instructions for completion of recording form

1. ONE FORM FOR EACH TREATMENT SESSION
Please complete one form for each treatment session given to patients included as subjects in the Functional Strength Training lower limb clinical trial
2. TO COMPLETE THE AIMS SECTION
Please place a tick in the box which best describes the aims relevant to the particular treatment session being recorded
3. TO COMPLETE THE GROSS POSITION SECTION
Please place a tick in the box for every gross position used to deliver physiotherapy treatment during the treatment session being recorded
4. TO COMPLETE THE EQUIPMENT SECTION
Please place a tick in the boxes which best describes the equipment used during the particular treatment session being recorded
5. TO COMPLETE THE SECTION "SPECIFIC PHYSICAL THERAPY INTERVENTIONS"
Please place a tick in the boxes which best describe the treatment that was given to the patient during the particular treatment session being recorded.
6. FOR FURTHER DESCRIPTION OF ITEMS ON RECORDING FORM OVERLEAF
Please refer to the accompanying document "Description of Lower Limb Treatment for Patients in FST Trial"
7. COMPLETED FORMS GIVEN TO RESEARCH TEAM
When forms are complete please pass to a member of the research team

Abbreviations for and glossary of terms used in recording form

Act	Activity/activities
Environmental surface	A surface to enhance sensory input during functional activity e.g. sitting on a block of foam, walking on an exercise mat, walking on uneven ground
Facilitation	The application of an appropriate mode and dose (frequency, duration and intensity) of sensory stimulus provided by the therapist to access a desired active response from the patient
Funct	Function/functional
High hold/surface	A surface level with at least the mid-thoracic point of the patient to provide a hold and/or security during physical therapy intervention
Imagery	Mental rehearsal of a motor act that occurs in the absence of overt motor output
Low hold/surface	A surface level between the hip and mid-thoracic point of the patient to provide a hold and/or security during physical therapy intervention
Mvmnt	Movement
Physiotherapist	Person with professional Physiotherapy qualification
PT	Physical Therapy
Re-ed	Re-education
Rehabilitation Assistant	Person assisting the physiotherapist but who is not a qualified physiotherapist (e.g. student, nurse, technician, carer)

Appendix 2 Training update days for research therapists

Training in delivering each of the trial interventions, MPT and FST, was provided for all research therapists employed to deliver the trial intervention; this was initially completed before the first participant was recruited at each site. Each therapist was ultimately allocated to one intervention only and undertook specific training in the allocated intervention. However, it was important that each therapist also had an awareness of the non-allocated intervention in order to fully understand the differences and similarities between each intervention/approach (MPT and FST) and, therefore, the parameters of each of the trial interventions.

During the trial there was a turnover in research therapist staffing, and as each new research therapist came into post during the trial, this initial training was also provided on an individual basis with subsequent and ongoing peer mentorship and networking from the research therapists delivering trial intervention at the other sites.

In addition to initial training, two training update days were held during the recruitment phase of the trial. All research therapists employed to deliver trial intervention at that time attended these sessions. Both training update days were held in London over a period of 2 consecutive days. Through these update days, the within-trial research therapist networking was maintained and enhanced, enabling the research therapists to consult regularly with their peers providing the same trial intervention, but in different centres, to talk through understandings and practice. The trial manager and two of the other authors, Susan Hunter and Valerie Pomeroy, were also involved in these networking conversations.

Training update dates: 7 November 2013 and 6–7 July 2015.

Venue: both training update days were held in London, one at UEA London (November 2013) and another at the Premier Inn Hotel, London Victoria (July 2015).

Facilitators/trainers: Valerie Pomeroy and Susan Hunter.

Programme/content of the day: see programmes to follow.

Format: open structured discussion, small-group work with whole-group feedback and discussion (see following for summary of discussion and key actions/decisions agreed by the team).

FAST-INDICATE training: delivering trial intervention – November 2013, UEA, London

Day 1

Session 1: 11.15–13.30

1. Plan for the day.
2. Experiences of delivering therapy so far – whole-group discussion.
3. Identify specific topics for the 2 days – whole-group discussion.
4. MPT and FST groups – discussion around therapy for various patient presentations and problems:
 - a. low/high tone
 - b. shoulder subluxation/pain

- c. low/high ability
 - d. cognitive/perceptual problems
 - e. somatosensory loss.
5. Feedback from groups on therapy delivered by each team for a patient with low tone/low ability; discussion of differences between the two approaches (e.g. hands-on/hands-off; starting position/postural control).

Lunch 13.30–14.15

Session 2: 14.15–16.15

1. Feedback and discussion about therapy for the high-ability patient, particularly issues related to dexterity and progression for both MPT and FST.
2. Discussion/clarification around fundamental differences between MPT and FST, and how they might appear to be similar but remain different (e.g. progressive strengthening vs. task practice, strength vs. endurance, feedback, facilitation vs. guidance vs. active-assisted exercise) and what is a 'middle therapy' (i.e. neither MPT nor FST) (e.g. immersion of limb in water bath/'hydrotherapy'/use of hydrotherapy principles such as buoyancy/effect of temperature on tone and pain/stiffness).

Day 2

Session 3: 9.00–10.30

1. Self-directed therapy – what is involved, how is it monitored, how are instructions communicated to participants, how is it recorded, what is appropriate content, overcoming cognitive/memory difficulties, leaving equipment with patients and related issues of blinding, etc.

Session 4: 11.00–12.30

1. Documentation of therapy – inclusion of number of 'reps'?
2. Adverse event reporting.
3. 'Middle therapies' that are neither MPT or FST, for example hydrotherapy, pulleys, FES.
4. Feedback/evaluation.

12.30 Lunch and close

Topics identified for discussion and actions agreed during the training

1. Therapist-directed and participant-administered therapy.
 - Specific equipment that was required for FST would be provided by the research therapist. However, written instructions would not be provided by the therapist, but the participant or carer could make notes to remind them of what exercises they should do, and when/how often they should do them.
 - It was noted that hand dominance and side of hemiplegia potentially impacted on the ability to complete this participant-administered therapy.
 - The presence/involvement of a carer or spouse was likely to be helpful in participants administering their own therapy/exercises.
 - Variability and non-standardisation of this directed therapy was important because of personalised care.

2. Equipment left at participant's house for directed therapy.

- There is a potential threat to blinding if equipment that is obviously specific to FST is left at the participant's home and seen by the clinical team. Its presence may confound the content of CPT, as the clinical team might be tempted to use this equipment in their CPT programme with that participant, thus increasing the dose of FST and changing the nature of actual CPT.
- There was a suggestion that the content of CPT should be analysed for both groups to see if it is affected by group allocation (i.e. whether or not there is more strength training activity for the FST group), which might be a result of the presence of strengthening equipment in the home.

3. Documenting therapy.

- It was agreed that the number of repetitions of an exercise/activity in the FST group would not be reported.

4. Progression of dexterity activities in high-functioning participants.

- This was discussed in the context of generating ideas for progression exercises to improve dexterity in high-functioning participants and the difficulty this presents was acknowledged.

5. Difference between strength and endurance training/activities in FST.

- Discussed and number of repetitions for strengthening to be based on six repetition maximum, whereas number of repetitions for endurance to be based on three sets of 10–12 repetitions.

6. Use of feedback and the difference between knowledge of performance and knowledge of results.

- Knowledge of performance is characterised by a focus on movement (body part, direction/plane, e.g. bend, straighten elbow), whereas knowledge of results is characterised by a focus on quantitative measure of goal achievement (e.g. moving an object a set distance).

7. Use of active-assisted exercise/movement and facilitation in FST.

- Neither active-assisted nor facilitated movement is acceptable as part of FST; however, providing support to a body part in order to minimise the effect of gravity as part of a progressive strengthening regime is acceptable as long as the support is simply supporting the weight of the limb and not assisting with movement.

8. Adverse event reporting.

- Pain and fatigue are to be monitored at each therapy visit to identify adverse reactions to the therapy:
 - A change in two levels on the Motricity Index that occurs on four consecutive occasions is to be considered an adverse reaction of fatigue (AE on the CRFs).
 - The presence of new pain over four consecutive occasions is to be considered an adverse reaction of pain (AE on CRFs) only if the pain cannot be explained by the clinical team as resulting from a different cause. If a participant reports new pain, the research therapist or PI will contact the clinical team to determine whether the new pain is likely to be caused by the trial intervention or if there is another explanation for that pain. If that new pain is present on four consecutive visits by the research therapist is considered to be attributable to the trial therapy, then an AE form should be completed. If the pain is not considered to be attributable to the trial intervention, then it is not necessary to complete an AE form but an e-mail trail of the discussion with the clinician should be kept and stored.
 - If there is pre-existing pain at the start of the trial, this should not be recorded on the pain and fatigue form; a record should be made of this pain only if it changes in intensity or nature.

9. Use of 'special' equipment and 'middle therapies' that could constitute a different intervention.

- It was agreed that neither pulleys, nor FES, nor water bath/hydrotherapy should not be used for MPT or FST exercises.
- TheraBand® (TheraBand, Akron, OH, USA) is acceptable for strength training as part of FST.
- Throwing and catching a ball is an acceptable activity for FST or MPT; however, the use of the ball and progression of exercise would be subtly different for each intervention.

Training evaluation: research therapists, UEA, 7 November 2013

After the training had been completed in November 2013, the research therapists and trial manager were asked to summarise what they had gained most from the training. The following were the verbal responses received:

- Greater understanding of the trial interventions – able to now differentiate between MPT and FST. This was reassuring and insightful.
- Astounded by the quality of the team.
- Reaffirming similarities of therapy between centres.
- Team building – knowing everyone better.
- Getting to know people; links for further discussions.
- Discussion at length to clarify treatment – clinically reason choices.
- Clarification re MPT and function and scope of what can be done.
- New ideas for new members of the team.
- Insight into MPT.
- Increased scope of what can be done in MPT and FST.
- Clarification re paperwork, especially AEs.
- Focus on feedback given to patients.
- Increased treatment options.

FAST-INdICATE training: London, 6–7 July 2015

Day 1: Monday 6 July 2015

1. Plan for the day.
2. Experiences of delivering therapy so far: good and not so good – whole-group discussion.
3. Identify specific topics for the 2 days – whole-group discussion.
4. MPT and FST groups – discussion around therapy you would deliver for:
 - a. Patient with low tone
 - b. Patient with high tone
 - c. Patient with shoulder subluxation/pain
 - d. Low-ability patient
 - e. High-ability patient
 - f. Patient with cognitive/perceptual problems
 - g. Patient with somatosensory loss.
5. Feedback from groups on therapy delivered by each team for patient with low tone/low ability; discussion of differences between the two approaches (e.g. hands-on/hands-off); starting position/postural control.
6. Feedback and discussion about therapy for the high-ability patient, particularly issues related to dexterity and progression for both MPT and FST.

Day 2: Tuesday 7 July 2015

1. Val Pomeroy to present an update on the mechanisms of recovery and predictors of stroke rehabilitation response.
2. Discussion/clarification around fundamental differences between MPT and FST, and how they might appear to be similar but remain different (e.g. progressive strengthening vs. task practice, strength vs. endurance, feedback, facilitation vs. guidance vs. active-assisted exercise); and what is a 'middle therapy' (i.e. neither MPT nor FST) (e.g. immersion of limb in water bath/'hydrotherapy'/use of hydrotherapy principles such as buoyancy/effect of temperature on tone and pain/stiffness).
3. Self-directed therapy – what is involved, how is it monitored, how are instructions communicated to participants, how is it recorded, appropriate content, overcoming cognitive/memory difficulties, leaving equipment with pts and issues of blinding, etc.
4. Claire and Liz to lead a discussion on trial assessment procedures.
5. Feedback/evaluation.

Close

Appendix 3 Description of movement performance therapy

The trial intervention MPT was formerly referred to as the control intervention CPT in our earlier trials and publications, and the content of MPT remains the same as for CPT described earlier in this paper. This intervention is intended to reflect a typical UK physiotherapy treatment for stroke. MPT emphasises therapy interventions provided by a therapist using predominantly hands-on facilitation and guiding movement (therapist dependent) to provide somatosensory stimulation and to optimise joint and body part alignment in preparation for voluntary movement. Some iterative practice of functional tasks is included but without systematic progression in resistance to movement or repetition. A manual was produced to support therapists delivering MPT, which clarifies terminology, etc. This has been appended in this section. The TIDier checklist format has been used to summarise and describe MPT (*Table 35*).

TABLE 35 Summary and description of MPT

Brief name	MPT
Why? Describe any rationale, theory or goal of the elements essential to the intervention	<p>MPT is a part of established CPT, which is supported by a very limited research evidence base. MPT therapy content was first developed through literature reviews and iteratively with senior, experienced neuro-physiotherapists, who described in detail the therapy techniques and interventions they used in routine UK clinical practice to retrain sensorimotor function and movement in the hemiplegic upper limb following stroke; from this description, a schedule of treatment was developed and validated to provide a way of recording the content and amount of MPT provided for people presenting with upper limb motor impairment after stroke (Hunter <i>et al.</i>, 2006;⁶⁸ Donaldson <i>et al.</i>, 2009⁴⁶). MPT is focused on:</p> <ol style="list-style-type: none"> 1. Improving the quality and normality of movement in terms of fluidity (smoothness), co-ordination of upper limb segments and minimisation of effort to achieve efficient functional movement 2. Postural control and joint and muscle alignment in preparation for voluntary movement 3. Therapeutic handling (tactile cues through manual contact) to facilitate or inhibit motor system activity underlying the performance of movement required for functional tasks <p>The purpose of the various techniques that together make up the 'module' of MPT include:</p> <ul style="list-style-type: none"> • Enhance recovery of sensory function and ability • Enhance musculoskeletal alignment and range of motion • Enhance the production of appropriate muscle activity in the paretic and non-paretic upper limb • Prevent or reduce pain and other secondary complications • Enhance recovery of the quality and normality of voluntary movement in terms of fluidity (smoothness), co-ordination of upper limb segments and minimisation of effort • Enhance recovery of postural control • Enhance recovery of transport ability of the paretic arm • Enhance recovery of manipulative ability of the paretic hand

continued

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
<p>What?</p> <p>Materials: describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL)</p> <p>Procedures: describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support</p>	<p>Quality of movement is emphasised during performance of a task. Participants are encouraged to practice activities such as grasp/release, reaching to objects, pointing in space, but not always as part of a specific functional task. During these activities, the therapist monitors and regulates quality of postural alignment and voluntary movement using hands-on techniques</p> <p>Before any voluntary movement is attempted by the participant, the therapist uses appropriate techniques to ensure that participants are in the optimum gross body posture for the movement, and that the joints and segments of the upper limb are in the correct alignment. During the voluntary production of movement, the therapist will use 'hands-on' techniques to maintain the optimal posture and alignment for the specific activity. Moreover, treatment activities are used in combination; for example, a participant might perform voluntary reaching for a cube, and the therapist may have provided some stroking to the skin overlying the forearm extensor muscles, and passive movement of the elbow joint, as a precursor to the voluntary movement. This would have been to provide sensory stimulation to the limb and increase the participant's awareness of/attention to the limb segments and joints that need to be controlled during that movement. The therapist might also provide some active assistance during the reaching movement to ensure that the movement was smooth. Thus, the treatment activities are designed to be used in different combinations for different individuals depending on their ability to produce high-quality voluntary movement</p> <p>Treatment progression is determined by the therapist using clinical reasoning to inform how to change within and between activities to improve the production of quality movement. The process of clinical reasoning incorporates a range of variables including participant motivation, cognition, mood, response to previous activity and long term goals. Resultant clinical decisions may include changing the objects used, the spatial-temporal framework for movement, the focus of the activity and the activities themselves. There is no systematic progression in terms of objects, treatment activities or number of repetitions of an activity. Indeed, the emphasis is the production of quality movement underpinning normal performance of everyday functional tasks which need to be performed in different environmental contexts</p> <p>Motivation through goal-setting</p> <p>It is essential that participants feel motivated to engage in the intervention. Goal-setting can enhance motivation and clinical guidelines stress that it is an integral part of stroke rehabilitation (RCP, 2016⁶⁹). Therefore, the therapist and participant will discuss the activities that will be prioritised and document these on the intervention record sheets</p> <p>Engaging in therapeutic activities</p> <p>The therapist assesses the participant's ability to perform a movement, such as reaching for a therapeutic object (ball/block/cone) and notes the movement components that are difficulty to perform with normal quality. The therapist will also note the blocks to quality movement. This assessment is based on expert knowledge of normal movement sequences and postural control. Clinical reasoning is employed to determine which components/elements are deficient for individual participants at different times in their recovery after stroke</p> <p>Practice</p> <p>Assessment would start with whole practice of a functional task with a therapeutic object to enable the therapist and participant to identify which components (if any) can be performed normally (with quality). Whole practice is only used if the participant is able to produce quality movement throughout. This may enhance motivation especially if used to emphasise how much improvement has been made. However, it will often be the case that hands-on therapy techniques are required to produce quality movement and, in this case, activity should focus upon the components that are problematic. When possible, the activity session should ideally finish with whole practice to enable the participant to put the components into context, and practice the dynamics of a task as a whole (and thus the entire motor programme)</p>

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
	<p>Constant practice involves the repetition of identical movement; variable practice involves practice of different variations of the same category of movement. Movement patterns underlying everyday functional activities are inherently variable, so MPT will encourage variable practice by, for example, using different start and end points (e.g. reaching in different directions), movement from different postures (e.g. sitting/standing) and using different therapeutic handling techniques</p> <p>Feedback</p> <p>Augmented feedback (i.e. feedback provided by the therapist) is one of the most important influences in the process of acquiring movement skill and, therefore, its application needs to be carefully considered (Schmidt and Lee, 1999;⁷⁰ Magil, 2001;⁷¹ Wulf <i>et al.</i>, 1993⁷²). Augmented feedback pertains either to the quality (pattern) or the outcome of the movement:</p> <ol style="list-style-type: none"> Feedback about the movement pattern is known as knowledge of performance; an example is stating to a participant that they bent sideways during reaching Feedback about the movement outcome is known as knowledge of results; for example, telling a participant how long it took them to reach for the object <p>MPT feedback emphasises knowledge of performance. This emphasis will encourage an internal focus on the body parts involved in producing quality movement. The therapist will give prominence to the provision of information for movement and feedback during its performance through tactile input during therapeutic handling. For example, during active-assisted movement the therapist may guide the path taken by the hand during a reaching activity and thus provide sensory input to the participant about how the speed and direction required for quality movement. Any verbal feedback provided will direct the participant's attention to the guidance from the therapist's hands. Emphasis will also be given to encouraging participants to focus on how the movement feels and how individual joints/segments of the body are moving. For example, during reaching forwards, feedback could be given on movement of the elbow rather than the success of grasping the target (e.g. 'next time keep you elbow closer to your body'). As the content of feedback depends on the performance of each individual participant, no attempt is made to standardise this. It is a strong requirement, however, that the research therapist is an expert in therapeutic handling with extensive knowledge of, and clinical experience in, the science of normal movement</p> <p>Amount and frequency of feedback</p> <p>A faded feedback schedule is recommended, whereby feedback is given frequently in the early stage of learning, and less frequently as the participant progresses (Schmidt and Lee, 1999;⁷⁰ Magil, 2001⁷¹). As participants benefit from self-learning, progressively decreasing feedback enables independent problem-solving to enhance motor learning; for MPT, participants will be aware of when their movement quality is improving as the therapist will reduce the amount of time during a session where tactile contact and guidance are provided. Another strategy of fading feedback is by providing bandwidth feedback; this refers to feedback provided only when performance falls outside the specified criteria. For example, a person with stroke may use their trunk to reach forward for a cup. The therapist may want to discourage this compensatory movement and stimulate active shoulder flexion instead. By touching the participant's trunk if this moves forward, the participant will realise their mistake. Note that they only receive this feedback if they do something wrong, otherwise practice continues with the participant knowing their performance is correct. This type of feedback promotes consistency of performance</p> <p>Periodically, it is recommended that a summary of feedback or an average feedback score is provided to the participant, formulated in constructive terms. An example of summary feedback is the number of times out of five attempts that the movement was performed correctly. An example of average feedback is the average number of times that the participant has their elbow by their side while lifting an object five times. Both of these methods mean that feedback is not provided after each attempt, but only after a certain number have been completed. Both summary and average feedback are postulated to be more effective than feedback provide on every attempt by providing the learner with an opportunity to process their intrinsic feedback and reduce reliance on augmented feedback</p>

continued

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
	<p>Focus on feedback</p> <p>Feedback can induce an internal focus of attention in the learner (about the body and body parts) or an external focus of attention (about effects of the movement on the environment). Although an external focus feedback may be more effective than internal focus feedback in healthy people (Wulf and Prinz, 2001;⁷³ McNevin <i>et al.</i>, 2003⁷⁴), it remains uncertain whether or not this is generalisable to stroke survivors. Participants can be provided with some essential external focus information in order to ensure they understand the purpose of the activity, but the emphasis is on an internal focus of attention</p> <p>Order of activities in each intervention session</p> <p>Assessment should commence with the whole practice of a functional movement, using a therapeutic object, to enable the therapist and participant to identify which components (if any) can be performed normally (with quality). Activities and exercises are chosen from the selection contained in the Treatment Activities section of the Manual (see following), using clinical reasoning to determine the content of the intervention session. There is no predefined order for treatment activities within MPT</p> <p><u>Specific therapy activities</u></p> <ol style="list-style-type: none"> <i>Soft tissue mobilisation</i> <ol style="list-style-type: none"> Stroking Effleurage Lymph drainage techniques Petrissage (kneading/wringing/picking up/rolling) Specific compression (trigger points) Myofascial release Frictions <i>Joint mobilisation</i> <ol style="list-style-type: none"> Active movements, not functional Passive movements Accessory movements <i>Facilitation of muscle activity/movement</i> <ol style="list-style-type: none"> Mental imagery Patient-generated cueing Therapist-generated cueing Hands on to induce a desired motor response Active-assisted movement Facilitation of arm/hand activity from another body part Restricted use of non-paretic limb <i>Positioning</i> <ol style="list-style-type: none"> Side lying hemiplegic side Side lying non-hemiplegic side Supine lying Half lying Sitting in armchair Forwards lean sitting Sitting in wheelchair

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
	<p>5. <i>Specific sensory input</i></p> <ul style="list-style-type: none"> i. Tactile stimulation (e.g. textures, temperatures, vibration, stroking) ii. Proprioceptive stimulation (e.g. joint distraction/compression, stereognosis exercises) <p>6. <i>Exercises to increase strength</i></p> <ul style="list-style-type: none"> i. Resistance from the therapist ii. Resistance from body weight iii. Resistance from equipment iv. Gravity-neutral repetitive movement <p>7. <i>Balance and mobility incorporating upper limb activity</i></p> <ul style="list-style-type: none"> i. In or from lying ii. In or from kneeling iii. In or from sitting iv. In or from standing v. In walking <p>8. <i>Upper limb functional tasks</i></p> <ul style="list-style-type: none"> i. Bilateral functional activities ii. Unilateral reaching activities which are object directed iii. Unilateral reaching activities which are spatially directed iv. Dexterity exercises (including all grasp and manipulation activities, such as writing or picking up small objects such as pins/marbles) <p>9. <i>Education for patient and/or carer</i></p> <ul style="list-style-type: none"> i. To encourage self-monitoring of upper limb with awareness of positioning and alignment ii. Transfers training iii. Limb handling and positioning skills iv. Written/visual/photo exercise programme <p><i>Examples of equipment used:</i></p> <ul style="list-style-type: none"> • Air inflated supports • Ball • Balloon • Beads • Bed • Chair • Coins • Comb/hairbrush • Games (Jenga, dominoes, chess, draughts, jigsaw puzzle, cards) • Gymball • Jug • Multigym • Parallel bars • Pens/pencils • Pillows • Plinth • Sandbag • Sensory box • Small ball • Table/high table • Tennis ball, football • Theraband

continued

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
	<ul style="list-style-type: none"> • Toothpaste, deodorant • Towels • Upper limb bike • Wedge
<p>Who provided?</p> <p>For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given</p>	<p>MPT is delivered by therapists, providing a strong emphasis on ‘hands-on’ techniques (therapeutic handling). The therapy is therefore therapist dependent, with an emphasis on preparation and joint alignment via tactile/proprioceptive input. For the FAST-INDICATE trial, MPT was provided by qualified senior (UK band 6) physiotherapist or occupational therapist, or by a junior (UK band 5) therapist under the supervision of a band 6 therapist. UK ‘band 6’ is an indication of some specialised experience post qualification. Specific training was given to all trial therapists in understanding the philosophy behind the intervention, the content of the intervention and how to deliver the intervention. Training was provided for the group of therapists, and was also provided on an individual basis. Two follow-up training events were provided for therapists employed to work in the trial</p>
<p>How?</p> <p>Describe the modes of delivery (e.g. face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group</p>	<p>Therapy was delivered face to face with the trial participants; for the majority of treatments, this was on an individual basis. A small number of treatments were provided in a group situation but the therapy content was personalised. In addition to face-to-face therapy, some therapist-directed but participant-administered therapy was delivered; the therapist advised the participant about which exercises or activities should be done, how they should be done, and for how long (intensity, frequency and duration). For example, this might include massage and manipulation of the hand, and practice moving joints and digits in the arm and hand in a controlled manner</p>
<p>Where?</p> <p>Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features</p>	<p>MPT intervention was provided in the hospital ward, hospital out-patient facility or in the participant’s own home</p>
<p>When and how much?</p> <p>Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose</p>	<p>The MPT intervention was delivered for up to 120 minutes per day, Monday to Friday, for 6 weeks; this did not include bank holidays. This amounted to a maximum of 30 sessions of treatment. When the participant was not able to tolerate 120 minutes of therapy in one block of treatment, he or she was provided with directed therapy that he or she could self-administer later in the day to achieve the 120 minutes of therapy. An MPT treatment schedule was provided for the therapists to record the content and intensity (number of minutes) of treatment each day. A trial operating procedure or treatment manual was provided for therapists to refer to for clarification and guidance. The treatment schedule and manual are appended (see <i>Appendices 4</i> and <i>5</i>)</p>
<p>Tailoring</p> <p>If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when and how</p>	<p>The intervention was personalised according to the clinical presentation of the participant each day; clinical decisions were made according to the participant’s sensorimotor performance/ability and the most-appropriate interventions from the MPT treatment schedule were selected in an appropriate combination determined by the skilled therapist. Choice of activities by the therapist is informed by expert assessment of how much quality voluntary movement can be performed by a participant, where this becomes difficulty during a functional task, and why this happens. Delivery of treatment activities is targeted at reducing the blocks to, and enhancing the performance of, quality movement. Choices are based on a process of clinical reasoning and problem-solving in relation to the identified movement problem. This process is undertaken in consultation with individual participants to ensure adherence to the principles of goal-setting</p>

TABLE 35 Summary and description of MPT (*continued*)

Brief name	MPT
<p>Modifications</p> <p>If the intervention was modified during the course of the study, describe the changes (what, why, when and how)</p>	<p>Initially, MPT was referred to as CPT (as detailed in the trial protocol); however, following further discussion with clinical colleagues, the trial intervention was renamed MPT because it did not represent all aspects of CPT but focused on movement performance in the upper limb</p>
<p>How well?</p> <p>Planned: if intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them</p> <p>Actual: if intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned</p>	<p>Intervention adherence/fidelity was assessed by two members of the Trial Management Group (VMP and SMH) who observed both trial interventions being provided to participants at two of the three sites during the trial. In order to maintain fidelity, training events were organised for all therapists providing trial intervention, and an internal network for the therapists was set up so that they could seek peer support and mentorship regarding intervention fidelity</p>

Appendix 4 Statistical analysis plan

FAST INDICATE STATISTICAL ANALYSIS PLAN FOR THE FINAL ANALYSIS

Study Title: Clinical efficacy of functional strength training for upper limb motor recovery early after stroke: neural correlates and prognostic indicators



Short Title: FAST INDICATE

IDs: EME reference 10/60/30

Funded by: MRC and NIHR

Protocol Version: FI trial protocol 7 3_20150515.pdf

SAP Version: Version 1.0 Date: 15/09/2016

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Stroke is the single largest cause of adult disability worldwide. Each year, in England alone, approximately 110,000 people suffer a stroke and approximate annual costs are: £2.8 billion direct health and social care costs; £1.8 billion to the wider community in terms of lost productivity and disability; and £2.4 billion in costs to informal carers. The majority of this cost is the result of "rehabilitation and life after stroke". The impact on the NHS is unlikely to fall because the benefits of better preventative and acute care are likely to be offset by an increase in the percentage of older people in the population to 23% in 2031 (16% in 2003), in whom most strokes occur. Stroke rehabilitation is a research priority for the NHS and more widely for Europe.

It is known that physical therapy for motor impairment after stroke is generally effective, that motor recovery occurs most rapidly in the first three months after stroke and that during this period the central nervous system (CNS) probably has most potential for reorganisation. Further progress in the provision of effective therapy for patients early after stroke requires deeper understanding of the process of CNS recovery associated with clinical improvement (mechanisms) and determining which physical therapies should be provided (clinical efficacy) for which stroke survivors (prognostic indicators).

Further progress, therefore, requires neurological investigation of the efficacy of well-characterised interventions for which proof-of-principle is established, and at the same time using these interventions to determine how the CNS responds in the presence of different stroke lesions. This is important because there is a need to establish knowledge of mechanism to improve understanding of why treatment works or does not work.

Investigating efficacy and mechanisms together in this Phase II trial will provide robust information to ensure that subsequent Phase III trials investigate the effectiveness of functional strength training (FST) targeted at the underlying CNS mechanisms of upper limb motor deficits early after stroke in those people most likely to respond. This approach is of critical importance in subsequent trials of neurorehabilitation interventions so that potentially important clinical effects are not diluted by attempting to treat patients for whom other interventions might be more appropriate. More generally, the results of this proposed trial, using conventional physical movement performance therapy (MPT) and FST as probes of CNS recovery, are expected to contribute to knowledge of the CNS mechanisms of upper limb recovery after stroke. The need for such research is well recognised.

1.2. STUDY OBJECTIVES

The primary driver for this research is the clinical hypothesis that FST for the paretic upper limb plus the standard amount of protocol-driven CPT (CPT+FST) produces greater improvements in motor impairment and functional ability and is more cost-effective than CPT+MPT in people with upper limb motor impairment early after stroke. The objectives are:

1. To determine whether CPT+FST commenced early after stroke produces greater improvements in upper limb motor recovery than CPT+MPT (clinical efficacy)
2. To identify the similarities and differences in the neural correlates of clinical improvement in upper limb motor function in response to (a) CPT+FST and (b) CPT+MPT (understanding neural and behavioural mechanisms)
3. To determine whether any pre-treatment parameters or any combination of pre-treatment parameters; (a) clinical severity, (b) anatomical location/volume of infarction (derived from structural brain imaging), (c) residual functional anatomy (derived from fMRI), (d) residual structural cortico-cortical and cortico-spinal connectivity (derived from DTI), and (e) brain-

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Statistical Analysis Plan

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muscle functional connectivity (derived from TMS), are sufficiently predictive of improvement in upper limb motor function to enable physical therapy to be targeted at those stroke survivors most likely to respond (new scientific/clinical principles)

A further objective on cost-effectiveness is not part of the Robertson Centre analysis.

1.3. STUDY DESIGN

The FAST INDICATE trial is a randomised, controlled, observer-blind, 2-group, multi-centre Phase II trial to determine efficacy of CPT+FST compared with CPT+MPT for enhancing upper limb recovery, with embedded explanatory measures to determine prognostic indicators for and neural correlates of response to CPT+FST and CPT+MPT.

Randomisation was stratified by clinical centre, time after stroke (up to 30 days and 31-60 days) and ability to use the paretic upper limb as assessed by the Nine Hole Peg Test (1 peg or less and 2-8 pegs).

1.4. SAMPLE SIZE AND POWER

The protocol (section ‘Sample size’) states:

The minimum clinically important change in ARAT score of around 6 points translates to an improvement of one level on 6 of the 19 upper limb tasks tested. There are no intra-class correlation coefficient (ICC) estimates in the literature for physiotherapy interventions being assessed using any of our proposed outcomes. ICC values are known to be lower where patient rather than process of care outcomes are being measured, with the ICC being expected to be somewhat lower than 0.05 for patient outcomes. This sample size calculation is based on actual ARAT data from our previous early phase trial. Assuming an ICC of 0.01 in both treatment arms and three centres with a separate therapist for each randomised arm, a sample size of 99 participants per group would have 80% power to detect a clinically important mean difference of 6.2 in ARAT change when analysing data using a two sample t-test, with Satterthwaite correction, applying a 5% 2-sided significance level and allowing for potentially different standard deviations in the CPT+MPT (7.9) and CPT+FST (19.3) groups. To account for clustering in the design (participants within therapist within randomised treatment at each study site) a sample size inflation factor $1+(m-1)*ICC$ is applied where m is the cluster size and ICC is the intra-class correlation coefficient. We have investigated this using the SSC software (Health Services Research Unit, University of Aberdeen). Here we have three study sites each with two therapists. Assuming that recruitment is evenly distributed across therapists, the sample size is therefore inflated to 129 evaluable participants per group. The corresponding mean differences in ARAT change that would be detectable in a study of this size for ICCs of 0.02 and 0.03 would be 7.0 and 7.8 respectively, showing that the design is fairly insensitive to assumptions about the ICC. Finally, to allow for an attrition rate of 10%, 144 participants per groups will be recruited – total sample size of 288.

1.5. DEVIATIONS FROM THE PROTOCOL

The protocol noted that the analysis methods to be employed would take into account the clustering aspect of the study. However, due to logistical issues the proposed clustering structure (patients within therapist within treatment group) was not carried out for all patients. Therefore the analysis methods noted in the protocol (which took account of the clustering) are no longer valid. All analyses will therefore be carried out as CPT+MPT vs CPT+FST with no clustering.

1.6. STUDY POPULATION

Potential study subjects were screened from either acute in-patient or rehabilitation settings in services provided around Birmingham, North Staffordshire and Norfolk.

1.6.1. INCLUSION CRITERIA (AS NOTED IN THE PROTOCOL)

1. adults aged 18+ years,
2. 2 - 60 days after stroke when they provide informed consent. This time period has been chosen because some people who may meet the criteria for this trial are discharged from stroke services a few days after stroke and they need to be provided with the opportunity to participate. As brain recovery occurs mostly in the first 3 months after stroke participants will be within what is considered to be the critical time window for neural re-organisation;
3. stroke in anterior cerebral circulation territory, cortical and/or subcortical, confirmed by clinical neuroimaging;
4. sufficient voluntary muscle contraction in the paretic upper limb to generate the beginning of prehension i.e score at least 11/33 for Motricity Index pinch section;
5. unable to complete the Nine Hole Peg Test (9HPT) in 50 seconds or less (maximum time for test);
6. no obvious spatial neglect as defined by a score of 0 or 1 on the Extinction and Inattention sub-scale of the NIH Stroke Scale.
7. have no obvious motor dyspraxia or communication deficits as assessed by ability to imitate action with the non-paretic upper limb. This will be assessed by the Research Therapist sitting alongside the potential participant. The Research Therapist will perform 5 upper limb activities and potential subjects will be asked to observe with intent to imitate and then perform the activities. The accuracy of imitation of observed activity will be assessed on the 3-point scale used by Decety[41]: 2 = correctly reproduced action; 1 = incorrectly reproduced action; 0 = not reproduced. Those scoring 8/10 or above will be considered to have the ability to imitate and therefore be included in this proposed trial;
8. were able, prior to the index stroke, to use the paretic upper limb to lift a cup and drink from it;

1.7. STATISTICAL ANALYSIS PLAN (SAP)

1.7.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out by the Robertson Centre for Biostatistics (RCB) for the final analyses of the FAST INDICATE study.

1.7.2. GENERAL PRINCIPLES

All study data will be summarised at entry to the study, after the treatment period (week 6) and after the follow-up period (month 6). Categorical variables will be summarised with the number and proportion of subjects falling in each category as well as the number missing. Continuous variables will be summarised using the number of observations, the number of missing values, mean, median, standard deviation (SD), lower quartile, upper quartile, minimum and maximum values.

All statistical tests will be performed using two-sided tests at the 5% level of statistical significance.

1.7.3. CURRENT PROTOCOL

The current study protocol at the time of writing is version 7.3, dated 15th May 2015. Any updates to the protocol after the approval of this version of the SAP, will be reviewed for their impact on this SAP, which will only be updated if the changes to the protocol require it. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.7.4. SOFTWARE

Data will be analysed using SAS for Windows v9.2 or later.

2. ANALYSIS

2.1. STUDY POPULATIONS

The randomised set (RS) consists of all randomised subjects who will be analysed according to the group to which they were randomly allocated.

2.2. BASELINE CHARACTERISTICS

No formal statistical analyses will be carried out on the baseline data. Baseline characteristics will be summarised for each randomised treatment group separately and overall.

The following baseline characteristics will be reported:

Demographic characteristics

- Age (years)
- Sex

Randomisation strata

- Time after stroke (≤ 30 days, 31-60 days)
- Ability to use paretic upper limb (1 peg or less, 2-8 pegs)
- Clinical centre

Medical History

- Type of stroke
- More paretic side of body
- Site of brain lesion

2.3. EFFICACY ANALYSES

2.3.1. FIRST OBJECTIVE - CLINICAL EFFICACY

To answer the first objective, the primary analysis will compare the change in the efficacy parameters (baseline and week 6) between the treatment groups.

Change in the efficacy parameters (ARAT paretic, ARAT non-paretic, Hand Grip Force, Pinch Grip force, Wolf Motor Function Test (WMFT) – total functional score and 15 individual functional scores, EQ-5D total score, EQ-5D VAS) at week 6 will be analysed using analysis of covariance (ANCOVA) models adjusted for the baseline value and randomisation strata (time after stroke, ability to use paretic upper limb, clinical centre). Adjusted least square means difference and 95% confidence intervals (CIs) will be reported.

Where the outcome distribution deviates from a normal distribution, a log or other appropriate transformation will be applied.

Changes from baseline at month 6 will be analysed as for week 6 changes.

2.3.2. SECOND OBJECTIVE – MECHANISMS (EXPLANATORY MEASURES)

To answer the second objective, associations between the changes in TMS and MRI variables will be compared to the changes in clinical efficacy measures (baseline to week 6). The clinical efficacy measures of interest are WMFT total score, ARAT – paretic, pinch force and grip force. Correlations will be carried out for the two treatment groups separately and for the groups combined:

The following TMS/MRI variables will be analysed:

- MRI: Volume of stroke lesion
- MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline
- MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS
- TMS: Motor Evoked Potential (MEP) – Biceps paretic (percentage of stimulator output at threshold)
- TMS: MEP – Extensor Carpi Radialis paretic (percentage of stimulator output at threshold)
- TMS: Motor Evoked Potential (MEP) – Biceps non-paretic (percentage of stimulator output at threshold)
- TMS: MEP – Extensor Carpi Radialis non-paretic (percentage of stimulator output at threshold)

In addition, the above TMS and MRI data at baseline, week 6 and change will be summarised and compared between the two treatment groups.

2.3.3. THIRD OBJECTIVE – MECHANISMS (EXPLANATORY MEASURES)

To answer the third objective, subgroup analyses will be carried out for the change in ARAT paretic at week 6.

The subgroups of interest are the following baseline variables:

- MRI: MNI CST Affected (yes/no)
- MRI: Volume of stroke lesion (above/below median)
- MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline (above/below median)
- MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS (above/below median)
- TMS: MEP – Biceps paretic (yes/no)
- TMS: MEP – Extensor Carpi Radialis paretic (yes/no)

The treatment effect will be calculated within each level of the subgroup (adjusted as for the first objective) and an interaction term for randomised treatment and baseline covariate will be included in the model.

2.4. SAFETY OUTCOMES

2.4.1. STUDY DISPOSITION

Patient disposition by treatment group will be reported with reasons for withdrawal from study:

- Adverse event (non-serious)
- Participant unwilling to continue in study activities
- Participant withdrew consent
- Participant withdrawn on advice of investigator
- Participant lost to follow-up
- Other

2.4.2. ADVERSE EVENTS

Adverse events will be reported in two phases: during the treatment period (start date on or after randomisation date and less than week 6 visit date) and during the follow up phase (start date on or after week 6 visit date).

Adverse events will be summarised by treatment group, ordered by system organ class and preferred term.

The following adverse events will be summarised:

- Adverse events
- Related adverse events
- Serious adverse events
- Unexpected serious adverse events

2.4.3. ADVERSE REACTIONS

The number and percentage of subjects with adverse reactions for pain and fatigue will be reported in two phases: during the treatment period and during the follow up phase (as defined for the adverse events in section 2.4.2).

3. DERIVED VARIABLES

Age is calculated as: (Randomisation date – date of birth)/365.25

ARAT will be calculated according to the validated score sheet.

Grip force and pinch force will be analysed as the maximum out of the (up to) three measurements taken at each visit.

Pain – reported on four consecutive visits (either behavioural or verbal) and this is confirmed as an adverse event during each phase

Fatigue – two consecutive visits where the fatigue is confirmed as an adverse event during each phase

Related adverse events – any adverse event reported with a causality of ‘definitely’, ‘likely’ or ‘possibly’ related. Events with a missing causality will be considered as ‘related’.

EQ5D score – each of the 5 questions are scored as 1, 2 or 3 in the case report form and the standard weighted score is assigned.

The weighted scores are calculated by subtracting the relevant weight coefficients from 1 (Perfect health). The constant term is used if there is any item with a response greater than level 1. The N3 term is used if any item is at level 3. For example, the algorithm for computing the score for the health state 21223 is:

$$1 - (0.081 + 0.069 + 0 + 0.036 + 0.123 + 0.236 + 0.269) = 0.186$$

4. DATA LISTINGS

No listings will be provided in the report. An excel file (or files) will be created containing all the data in the database (including derived calculations) to be sent to the Chief Investigator.

5. DOCUMENT HISTORY

This is version 1.0 of the statistical analysis plan, initial creation.

6. TABLE SHELLS

Protocol: FAST INDICATE

Population: Randomised

Table 1.1
Randomisation details, by treatment group and overall

Variable	Statistic	Treatment A (n= XXX)	Treatment B (n= XXX)	All (n= XXX)
Time after stroke	N	XX	XX	XX
	<= 30 days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	31-60 days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ability to use paretic upper limb	N	XX	XX	XX
	1 peg or less	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2-8 pegs	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Site	N	XX	XX	XX
	Birmingham	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Norwich	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Staffordshire	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Protocol: FAST INDICATE
Population: Randomised

Table 1.2
Demographic characteristics

Variable	Statistic	Treatment A (n= XXX)	Treatment B (n= XXX)	All (n= XXX)
Age (years)	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	Std Dev	XX.XX	XX.XX	XX.XX
	Median	XX.X	XX.X	XX.X
	Min - Max	XX - XX	XX - XX	XX - XX
	Interquartile range	XX - XX	XX - XX	XX - XX
	Missing	XX	XX	XX
Gender	N	XX	XX	XX
	Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Protocol: FAST INDICATE

Population: Randomised

Table 1.3
Medical history

Variable	Statistic	Treatment A (n= XXX)	Treatment B (n= XXX)	All (n= XXX)
Type of stroke	N	XX	XX	XX
	Ischaemic	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Haemorrhagic	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
More paretic side of the body	N	XX	XX	XX
	Left	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Right	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Side of brain lesion	N	XX	XX	XX
	Left	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Right	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Protocol: FAST INDICATE

Population: Randomised

Table 2.1a
ARAT during the study - non-paretic

Variable	Statistic	Treatment A (n= XXX)	Treatment B (n= XXX)	All (n= XXX)
Baseline	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	Std Dev	XX.XX	XX.XX	XX.XX
	Median	XX.X	XX.X	XX.X
	Min - Max	XX - XX	XX - XX	XX - XX
	Interquartile range	XX - XX	XX - XX	XX - XX
	Missing	XX	XX	XX
Week 6	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	Std Dev	XX.XX	XX.XX	XX.XX
	Median	XX.X	XX.X	XX.X
	Min - Max	XX - XX	XX - XX	XX - XX
	Interquartile range	XX - XX	XX - XX	XX - XX
	Missing	XX	XX	XX
Month 6	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	Std Dev	XX.XX	XX.XX	XX.XX
	Median	XX.X	XX.X	XX.X
	Min - Max	XX - XX	XX - XX	XX - XX
	Interquartile range	XX - XX	XX - XX	XX - XX
	Missing	XX	XX	XX

Similar tables to table 2.a:

Table 2.1b - ARAT paretic

Table 2.1c - Grip force

Table 2.1d - Pinch force

Table 2.1e - WMFT total score

Table 2.1f1 to 2.1f15 - WMFT functional scores

Table 2.1g - EQ5D score

Table 2.1h - EQ5D VAS

Protocol: FAST INDICATE

Population: Randomised

Table 2.2a

Change (Visit 2 – Visit 1) in ARAT non-paretic during the study

Visit 2 – Visit 1	Treatment	Number with data at both visits	Mean (std) at Visit 1	Mean (std) at Visit 2	Change, mean (std)	Least squares mean difference (95% confidence interval) of change between treatment groups	P-value
Week 6 – baseline	A	XX	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	X.X (X.X, X.X)	0.XXX X
	B	XX	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)		
Month 6 – baseline	A	XX	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	X.X (X.X, X.X)	0.XXX X
	B	XX	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)		

Only reported for subjects with data at both visits

Similar tables to table 2.2a:

Table 2.2b – ARAT paretic

Table 2.2c – Grip force

Table 2.2d – Pinch force

Table 2.2e – WMFT total score

Table 2.2f1 to 2.2f15 – WMFT functional scores

Table 2.2g – EQ5D score

Table 2.2h – EQ5D VAS

Protocol: FAST INDICATE
Population: Randomised

Table 2.3a
Correlations (change from baseline to week 6) for MRI: Volume of stroke lesion

Clinical Efficacy Variable	Statistic	Treatment A (n= XXX)	Treatment B (n= XXX)	All (n= XXX)
WMFT total score	Correlation co-efficient P-value	X.XXXX 0.xxxx	X.XXXX 0.xxxx	X.XXXX 0.xxxx
ARAT paretic	Correlation co-efficient P-value	X.XXXX 0.xxxx	X.XXXX 0.xxxx	X.XXXX 0.xxxx
Pinch force	Correlation co-efficient P-value	X.XXXX 0.xxxx	X.XXXX 0.xxxx	X.XXXX 0.xxxx
Grip force	Correlation co-efficient P-value	X.XXXX 0.xxxx	X.XXXX 0.xxxx	X.XXXX 0.xxxx

Similar tables to table 2.3a:

Table 2.3b - MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline

Table 2.3c - MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS

Table 2.3d - TMS: MEP - Biceps paretic (percentage of stimulator output at threshold)

Table 2.3e - TMS: MEP - Extensor Carpi Radialis paretic (percentage of stimulator output at threshold)

Table 2.3f - TMS: MEP - Biceps non-paretic (percentage of stimulator output at threshold)

Table 2.3g - TMS: MEP - Extensor Carpi Radialis non-paretic (percentage of stimulator output at threshold)

Similar tables to table 2.1a/2.2a (baseline and week 6 only):
 Table 2.4a/2.5a - MRI: Volume of stroke lesion
 Table 2.4b/2.5b - MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline
 Table 2.4c/2.5c - MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS
 Table 2.4d/2.5d - TMS: MEP - Biceps paretic (percentage of stimulator output at threshold)
 Table 2.4e/2.5e - TMS: MEP - Extensor Carpi Radialis paretic (percentage of stimulator output at threshold)
 Table 2.4f/2.5f - TMS: MEP - Biceps non-paretic (percentage of stimulator output at threshold)
 Table 2.4g/2.5g - TMS: MEP - Extensor Carpi Radialis non-paretic (percentage of stimulator output at threshold)

Similar tables to table 2.2b (ARAT paretic, baseline and week 6 only) will be produced for each level of the subgroup variables:

Table 2.6a – MRI: MNI CST Affected (no)

Table 2.6b – MRI: MNI CST Affected (yes)

Table 2.7a – MRI: Volume of stroke lesion (below median)

Table 2.7b – MRI: Volume of stroke lesion (above median)

Table 2.8a – MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline (below median)

Table 2.8b – MRI: Cortico-cortico anatomical connectivity: FA MNI corpus callosum midline (above median)

Table 2.9a – MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS (below median)

Table 2.9b – MRI: Cortico-cortico anatomical connectivity: Asymmetry ipsilesional:contralesional MNI CSTS (above median)

Table 2.10a – TMS: MEP – Biceps paretic (no)

Table 2.10b – TMS: MEP – Biceps paretic (yes)

Table 2.11a – TMS: MEP – Biceps paretic percentage of stimulator output at threshold (below median)

Table 2.11b – TMS: MEP – Biceps paretic percentage of stimulator output at threshold (above median)

Table 2.12a – TMS: MEP – Extensor Carpi Radialis paretic (no)

Table 2.12b – TMS: MEP – Extensor Carpi Radialis paretic (yes)

Table 2.13a – TMS: MEP – Extensor Carpi Radialis paretic percentage of stimulator output at threshold (below median)

Table 2.13a – TMS: MEP – Extensor Carpi Radialis paretic percentage of stimulator output at threshold (above median)

Appendix 5 Data management plan

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Data Management Plan Version 1.11

Study Title:	Functional Strength training for upper limb recovery after stroke
Study name:	FAST_INDICATE
Protocol No./Trial Registry No.:	N/a
Protocol Version No.:	Version 7.3 15 May 2015
Effective date:	14/03/16
Sponsor	University of East Anglia

Approval

Version 1.11

Prepared by:	Lorna Gillespie	Signature	Date
Approved by:	Sharon Kean	Signature	Date
Client review	Nick Leavey	Signature	Date

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1. Introduction

Overview

The aim of this document is to describe the roles, responsibilities and activities of the Robertson Centre for Biostatistics (RCB) as the Data Centre for the FAST INDICATE study commissioned by the University of East Anglia. All procedures and applications used will be in accordance with the RCB SOPs which are in accordance with current regulations.

1.2 Definitions and Acronyms

AE = Adverse Event
 ARF = Amendment Request Form
 CI – Chief Investigator
 CPT = Conventional Physical Therapy
 CRF = Case Report Form
 CTM = Clinical Trial Manager
 DM = Data Manager
 DMEC = Data Monitoring and Ethics Committee
 DMP = Data Management Plan
 Data Validation Plan = Outline of data validation testing as detailed in the Data Validation Specification
 Data Validation Specification = details of all data validation checks
 DQF = Data Query Form
 DSMB = Data & Safety Monitoring Board
 FST = Functional Strength Training
 ICH = International Conference on Harmonisation
 IMP = Investigational Medicinal Device
 ISD = Information Services Division
 IVRS = Interactive Voice Response System
 MQ = Manual Query
 MRI = Magnetic Resonance Imaging
 PI = Principal Investigator
 QC = Quality control
 QA = Quality Assurance
 RCB = Robertson Centre for Biostatistics
 SAE = Serious Adverse Event
 SAP = Statistical Analysis Plan
 SOP = Standard Operating Procedures
 TMG = Trial Management Group
 TMS = Transcranial Magnetic Stimulation
 TSC = Trial Steering Committee

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Personnel & Responsibilities

2.1 Overview

2.1.1 Sponsor

University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK

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2.1.2 Data Centre

The Robertson Centre for Biostatistics (RCB), University of Glasgow, Glasgow G12 8QQ will be known as the study Data Centre.

2.1.3 Project Co-coordinating Centres

Glasgow Clinical Trials Unit, University of Glasgow and Greater Glasgow & Clyde Health Board, Tennent Building, 38 Church Street, Western Infirmary, Glasgow G11 6NT

Norwich Clinical Research Trials Unit, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK

2.2 Data Centre

2.2.1 Data Centre Data Management Group (DMG)

Liz Anderson	Director Projects Administration
Sharon Kean	Director Information Systems
Dr Sarah Weeden	Project Manager
Lorna Gillespie	Lead Clinical Data Manager

Isobel Docherty	Data Manager
June Allan	Administrative Data Manager

Key project Contacts:
Michele Robertson Lead Statistician

2.3 Study contact details

Chief Investigator:

Professor Valerie M Pomeroy
Professor of Neurorehabilitation
Director of Research, School of Allied Health Professions
Acquired Brain Injury group
Faculty of Medicine and Health Sciences
Queen's Building
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ

Study Site co-coordinator:

Nick Leavey
School of Health Sciences, Room 1.21, Queen's Building,
University of East Anglia,
Norwich Research Park,

Robertson Centre for Biostatistics
Glasgow Clinical Trials Unit
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Norwich, NR4 7TJ

Email: [REDACTED]

Tel: [REDACTED]

Sponsor Personnel:

[Dannelle Breach](#),

Project Officer

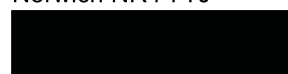
HSC

REN: Research & Enterprise Services

University of East Anglia,

Norwich Research Park,

Norwich NR4 7TJ



3 Study Details, Communication & Timelines

3.1 Study Objectives

To determine: the relative efficacy of FST+CPT and CPT+CPT; the neural correlates of improvement in response to FST+CPT and CPT+CPT; whether any one or combination of baseline measures predict improvement in motor function in response to FST+CPT or CPT+CPT; and estimate of cost-effectiveness to inform a subsequent definitive clinical trial.

3.2 Study Design

Randomized, controlled, observer-blind, 2-group multi-centre efficacy trial with embedded explanatory measures.

3.3 Data Analysis Plan

The Statistical Analysis Plan (SAP) is the responsibility of the study statistician.

3.4 Study timelines

See study details on Data Centre SharePoint site . GANT chart maintained by Nick Leavey.

3.5 Study communication

External communication will be mainly by email. Any significant decisions made during telephone conversations should be documented in an email from the Robertson Centre and sent to the client for confirmation. Teleconferences should be documented using the RCB meeting report template unless minutes of the meeting are to be supplied. These should be filed in the Data Management folder.

4 CRF Design

4.1 CRF design

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Glasgow Clinical Trials Unit
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Data capture is based on a paper CRF. The study CRF has been designed by the RCB according to SOP 06.001 and was fully reviewed prior to release by both Data Management and Statistics (SOP 06.002). The current version of the CRF in use is Version 1.1.

4.2 CRF revisions

Revisions of the CRF will be dealt with according to the CRF design guidelines (SOP 06.001, 06.002)

5 Data Sources

The Data Centre will be responsible for accumulating, reviewing and reporting on data from a number of primary and secondary sources.

5.1 Primary data sources

The primary sources of data arise from:

- a. Paper copies of study Case Report Forms (CRFs) completed at study site

5.2 Secondary data sources

Secondary sources of data arise from:

- a. Database Amendment Requests
- b. Responses to Data Queries

5.3 External data sources

The data centre will be taking receipt of third party data including the results of the following tests/procedures:

1. Transcranial Magnetic Stimulation (TMS)
2. Functional MRI
3. Structural MRI

Note: It is expected that the data centre will receive the final scores/data and not the raw source data

Data received by the Data Centre from external source/s will be logged and uploaded to the study database. These data will be considered to be a *copy* of the validated source data and any amendments must be made to the source data and the file/s resubmitted to the Data Centre.

6 Study setup

6.1 Overview

The study setup will begin at the Study Setup meeting at which the major project details, milestones and roles and responsibilities will be outlined and recorded in the Project Management documentation. A standard set of study folders will be created on the RCB filestore and both a test and 'live' database will be created. Project Management will be organised through a dedicated SharePoint Site which can be accessed by all members of the RCB Project Team.

6.2 Database setup

Details of the study database design and testing are held in the study setup folders according to SOPs 07.001, 07.011 and 07.013. The study database will reflect the structure of the study CRF and each data table will be created, tested and validated and authorised in the test database before release to the live

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system. The data dictionary will contain the following information and the current version will be available on the Data Centre filestore.

- Variable names
- Variable data types
- Derived data fields
- Data validation checks

The table structure and data processing issues are outlined in Appendix 1.

6.3 Study Identifiers

6.3.1 Subject Identifiers

A unique 6 digit Participant (screening) number will be allocated to each subject at the screening visit and will be used to identify the subject throughout the trial. The first 2 digits are unique to the study researcher doing the screening, and the last 4 digits are allocated sequentially by study researcher. If participant fails the screening process, they may be invited to return for re-screening. Note: a new screening number will be generated for each round of screening and any previous screening numbers will be recorded on the CRF. A randomisation number will be allocated via the IVRS and will be applied to the header on each page of the CRF.

6.3.2 Site numbers

There are 3 participating sites in the study:

- Birmingham – Site 1
- Norfolk – Site 2
- Staffordshire – Site 3

6.3.3 CRF Identifiers

Site number, Screening Number, Randomisation Number and Initials. Each CRF type will be identified by a form name and visit number (where appropriate).

6.3.4 Data Item Identifiers

Each data field will be given a name which identifies the data item on the CRF according to SOP 07.011. An annotated CRF maps the item on the CRF to the database variable.

7 Monitoring

7.1 Level of monitoring prior to delivery of CRFs to data centre

Timelines for monitoring and receiving CRF pages will be expected to be timely i.e. should be sent to RCB as soon as possible after monitoring has taken place. The current agreement is for data to be sent on or around the first Monday of the month. Initially, all CRFs will be reviewed by the CTM.

8 Recruitment

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288 participants will be recruited from the 3 sites. If informed consent is obtained, the patient will be screened and if suitable will be invited to return for the baseline visit at the end of which the participant will be randomised if eligible to participate in the trial.

9 IVR system

9.1 Overview

The IVR system (IVRS) will be a touch-tone telephone system which will allow trial sites to:

- Randomise a subject
- Review a subject

There is no requirement to monitor the system 24/7.
Further details can be found in Appendix 4.

9.1.1 Randomisation

A call must be made to the IVRS to randomise each subject. The system will allocate a treatment for the participant
An email with the participant's site number, screening ID, randomisation ID, and date of randomisation will be sent to CTM at the time of each randomisation.

10 Data Entry and processing

10.1 Overview

The Case Report Form (CRF) consists of demographics, medical history, eligibility test results, Eligibility criteria, functional test results, neuro-imaging status, TMS results, Randomisation details, Intervention details (CPT or FST), Resource use questionnaire, Pain/fatigue form, Adverse Event report, carer form, SAE report and withdrawal form

10.2 CRF Transfer to Study Data Centre

- Prior to transfer to the Data Centre, the CRF pages must be removed from the subject's binder, photo copied single sided and organised into batches accompanied by a CRF Transfer Forms (see Appendix 2).
- Where possible, all CRF pages for a given visit should be sent in the same batch. Forms for more than one visit can be sent in the same batch. Multiple screening visits are possible and screening visits will normally only be received accompanied by the baseline visit unless the subject is not suitable for inclusion in the study.
- CRF pages should be sent to the Data Centre as soon as possible after any required monitoring by courier or recorded mail.

10.3 Receipt and transfer form check at Study Data Centre

10.3.1 CRF checking

CRF pages will arrive at the Study Data Centre along with a Transfer Form and transferred to the Data Processing department where they will be placed in the study specific area. The completed Transfer Form information will be compared with the CRF pages received and any discrepancies will be flagged to the

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study site or via the monitors. Each CRF page attached for a subject will be checked to ensure all header information is complete and consistent and any discrepancies will be queried. If the information can be clearly identified from the other pages received then a working copy of the affected page/s will be made with the correct values to allow them to be processed. A query will be sent to obtain confirmation. The CRFs will also be checked for legibility and will be returned to site if illegible. Any subject identified CRFs will be returned to site immediately after working copies with any identifying information redacted are made to ensure processing of these forms is carried out.

10.4 Preparation for processing

All CRF pages will be scanned and logged using the RCB Document Management software.

Each CRF page will form part of a data processing batch. Each batch will be allocated a unique batch number and will contain a manageable number of CRF pages from several subjects, for a particular visit or CRF type.

10.5 CRF Data Entry

Batches of CRF pages will be entered and verified by a separate operator and a record of the entry details will be stored electronically. Numerical data are entered by the first operator and entered (blind) by the second (verifier). Any discrepancies are adjudicated by the verifier. Text data are entered by the first operator and the verifier makes a visual review of this and it is either accepted or updated. Data files generated at entry and verification are automatically archived by the Data Entry application and the verified data file uploaded into the Study database.

There are no study specific Data entry guidelines and all CRFs will be entered as seen. The batches will then be re-assembled into subject 'packs' and stored in locked cabinets in a restricted access room.

10.6 Data Amendment Forms

10.6.1 External amendment requests

A Data Amendment form (ARF) (see Appendix 3) will be used by the investigator, his/her designee or the study monitor to request a change to a CRF page that has already been sent to the Data Centre. These forms, each with a unique identifying number, will be reviewed by the Data Manager on receipt at the Data Centre, compared with queries already generated, and acted on as appropriate.

10.6.2 Internal amendment requests

An internal Data Amendment form (ARF) will be completed by the data manager for any data entry errors that require data updates to be made. All amendment requests will be checked and authorised prior to the database being updated.

10.7 Database Updates and Audit Trail

All changes to the study data will be authorised and a reason for the change given. Changes will be initiated by a resolved query or a database amendment request or internally via a change request. Details of all changes to the data will be stored electronically and the database record will be archived prior to any change to provide a complete audit trail. (SOP 07.015)

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11 Data Validation

11.1 Validation of Study CRF data

Validation checks will be created and run using the Data Dictionary application. Checks will include missing data, out of range values, illogical entries and invalid responses. Cross form checks comparing data items across different forms will also be performed. Details of the validation checks are documented in the study Data Validation Specification. Ranges will be agreed with the client and will be documented in the Validation Specification.

11.2 Validation Plan

The data checks detailed in the Validation Specification will be tested by (a) reviewing the Validation Specification against the CRF and (b) reviewing the Query Review output produced from the test data. All discrepancies will be reported, reviewed by the Lead Data Manager and any revisions re-tested.

11.3 Query generation

11.3.1 Automated Data Queries

Data validation will be carried out at intervals dictated by the receipt of data but will normally be within 2 working days after data entry. Failed validation checks will generate reports for review by a Data Manager. Each failure will be classified as a query, data entry error, do not query, invalid query or other reason.

Queries will normally be sent by email to the Study Coordinator within one week after receipt of CRFs. Data entry errors will be updated by the completion of an internal ARF.

11.3.2 Manual queries

Manual queries (MQ) may also be raised to enable other data issues that might arise to be queried (see Appendix 6 for a sample MQ).

11.4 Query Management

Queries will be produced from validation and cross form checks. The maximum number of queries per Data Query Form (DQF) will be one and each DQF will be uniquely identified by a sequential number. (See Appendix 5 for a sample DQF). Manual Queries (MQ) will be generated when required. (see Appendix 6 for a sample MQ). DQFs & MQs will be sent by e-mail as pdf files to the CTM.

11.4.1 Query resolution at site

All resolved queries will be returned to the Data Centre – by email or post. One copy only should be returned to the Data Centre, a copy must be kept at site and a copy held at GFA.

11.4.2 Data Centre

Emailed queries will be logged in the Document Management System and printed out for review. Hard-copy queries will be scanned and logged using the Document Management System.

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Resolved queries will be reviewed against the current data and marked-up where data updates are required. The marked-up queries will be reviewed by a second Data Manager and the updates made (see Section 10.7).

Queries will be tracked by the Data Centre and routine reports will be issued as required for outstanding queries that require resolution. Query tracking reports will be available by email.

11.5 Allowable Changes

Defined in the Allowable Changes document

12 Medical Coding

Medical coding will be carried out by trained personnel within the RCB according to SOP 07.006 and the General Coding Guidelines and will be subject to Quality Control procedures.

12.1 Study Specific Coding guidelines

None

12.2 Coding Medical Conditions

Data Sources:

- Adverse Events
- Serious Adverse Events

Note: The same version of the dictionary will be used throughout the study.

13 Safety data

13.1 Safety reporting

The study does not involve IMP and no safety reporting to the authorities is required.

14 Quality Plan

14.1 Quality control

Quality control procedures will be in accordance with the Data Centre's Standard Operating Procedures (SOP 13.005). QC is done at regular intervals and each QC batch is given a unique identifying number. The QC output will be reviewed by the QC committee along with error rate reports and any deviations from the RCB standard (error rates >0.1%) may result in additional checks being made. Data Entry errors identified during query review will also be updated and reviewed by the QC committee.

14.2 Quality Assurance

Quality Assurance will be carried out throughout the course of the study.

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14.1.1 Database creation

The design and testing of a new study database will be reviewed and approved by a senior member of the project team prior to release.

14.1.2 Query production

- The validation checks will be checked and approved as part of the Database Design phase
- Any changes to the validation checks during the course of the study will be approved by a senior member of the Data Management team.
- The query output will be QC'd for consistency and correctness of the coding procedure

14.1.3 Routine DM checks

The following are checks that do not form part of the routine data validation procedure and will be reported on the Centre's AdHoc report:

General DM checks

- Checks for duplicate records
- Checks for missing forms/CRF pages

Study specific data checks

Additional data management checks that do not form part of the routine data validation procedure will be carried out routinely e.g. Unscheduled and repeat visit date checks

14.1.4 Metrics gathering

The following metrics will be gathered to assess quality of the data capture.

1. Form processing metrics
2. Query processing metrics
3. Data entry error rates

14.1.5 End of Study QA

A full review of 5% of subjects CRFs will be carried out which will include all change request forms and queries. A detailed list of all CRFs, database updates and amendment requests will be checked against the stored patient CRF. The resulting report will be reviewed by a senior member of the Data Management Team and any actions resulting will be documented.

14.3 Problem reporting

Data issues and problems will be reported on a series of Data Centre Doc Notes. Each will be uniquely identified and indexed and stored in the Doc Note section of the Data Management folder and electronically in the study diary on the filestore. All will be reviewed by a senior member of the DMG. All other issues identified during the study will be recorded on a Data Management filenote. All filenotes will be recorded in the filenote index, copied with the original filed sequentially in the filenote section of the Data Management Folder and the copy in the relevant section of the Data Management folder.

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15 Reporting

The Data Centre will provide the following reports to the client via email on request.

Processing metrics

- Number of CRF pages received
- Number of forms entered

Query metrics

- Number of queries issued by type
- Number of queries outstanding

Quarterly Reports will be made available for the TMG, TSC and DMEC. For such reports a minimum of 28 days notice will be provided. The CTM and CI will discuss the requested contents of these reports with the various committees but should include blinded 132 randomization data, AE data, and a data summary on protocol compliance and data completion and quality.

For the DMEC, which will initially meet 6-monthly, an un-blinded version of the above should also be made available and sent directly from a RCB representative to the members of the DMEC. Details of such members and the dates of meetings will be provided by the CTM

16 Database Management & Security

16.1 Maintenance of user roles and access

16.1.1 RCB Database access

Access to the study database is restricted. User access is requested using the FAST INDICATE User Access request form which is held in study folder on filestore. These forms include a section where the type of access required can be specified

16.2 Database backup

The Data Centre will be responsible for the design, production, maintenance and back-up of the CRF database (see Section 20.4). This will include other applications that are required to manage the study data.

16.3 Modification to study database

Any change to the study database or any other data problem will be recorded on an RCB Doc Note which is identified with a unique, sequential number and is subjected to testing/review where required and authorised by a senior member of the DM team. All Doc Notes should be listed in an index to allow ease of review.

17 Study Closedown

17.1 Study closedown and database backup

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Glasgow Clinical Trials Unit
Doc Ref: Form_07.007a

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Study closedown will be carried out in accordance with SOP 07.017.

17.2 Study specific closedown issues

Closedown issues will be defined on the study closedown checklist which will be created as part of the study closedown process.

17.3 Archival

Archiving will be done in accordance with SOP 07.018.

17.5.1 Study Database Archive

A copy of the final database, in an agreed format, will be provided by the Data Centre to the sponsor at the close of the study (see Section 19.2).

17.5.2 Study CRF Archive

Study CRFs will be returned, from the Data Centre, to the sponsor at the close of the study for appropriate archival.

18 Internal Audit Plan

The Study system and its documentation will be audited according to the RCB audit schedule but should occur during the active phase of the study in accordance with SOP 12.001. Aspects of the study may come under other audit schedules relating to tasks e.g. coding, data entry.

19 External data transfers

19.1 Ad Hoc requests

Requests for data will be made by email to a member of the Data Management Group. The transfer will be documented in accordance with SOP 07.008 and the relevant document templates completed and approved by a member of the Senior Management Team.

19.2 End of Study Database Transfer

The study database will be exported to the sponsor in a format to be determined. Documentation will be provided and the export will be in accordance with SOP 07.008.

20 Software

20.1 Data Entry

SPSS Data Entry Module will be used for data entry, and data entry output data files will be stored as ASCII comma delimited text.

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20.2 Data management

20.2.1 Study Database

Microsoft SQL Server 2000 will be used for data management.

20.2.2 Data Management Applications

All significant DM applications will be developed in-house. Microsoft Visual Basic and Visual Basic.Net will be used for applications development.

Current applications in use:

- Data Dictionary application (ver 2.3)
- Manual query application (ver 1.21)
- Database Update application (ver 1.61)
- Form Processing application (ver 1.23)
- Coding application (ver 1.1)

20.3 Statistical Analysis

See the Statistical Analysis Plan (SAP).

20.4 Backup policy

The study database will be backed up daily. Tapes will be stored in a fire-proof safe every two days and stored off-site every seven days.

21 Computer Hardware & Operating Systems

21.1 Computer hardware

All computer hardware will be based on IBM PC compatibles.

21.2 Operating Systems

All operating systems will be from the Microsoft Windows 2000/XP family.

21.3 Documentation

The Data Centre will maintain its own Standard Operating Procedures and other documentation as is required for compliance with standards detailed in the ICH Guideline for Good Clinical Practice.

22 Standard Operating procedures

The SOPs adhered to are available on request.

23 Referenced documents

Allowable Changes document

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Document History

Version	Date	Description
Draft 1.0	16/08/2012	Initial creation
Draft 2.0	05/09/12	Incorporating SW comments & discussion with client
Draft 3.0	10/10/2012	Incorporating updated IVRS worksheet and Transfer form
Draft 4.0	05/12/12	Incorporating client feedback
Version 1.0	07/03/13	Release
Version 1.1	14/03/16	Minor changes: Study contacts and addition of SAE data to coding
Version 1.11	04/04/16	Change to Sponsor contact.

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Appendices

Appendix 1 Database details

	Form name	Pages	Template name	Visit/s
1	Visit 1, Screening	1-7	V01	1
2	Visit 2, ARAT	1-2	ART	2-4
3	Visit 2, Grip Force and Pinch Force	3-4	GPF	2-4
4	Visit 2, WMFT	5-6	WMF	2-4
5	Visit 2, EQ-5D	7-8	EQ5	2-4
6	Visit 2, Randomisation	9	V02	2
7	Visit 2, Neuro-imaging	10-11	NUI	2-3
8	Visit 2, TMS	12-17	TMS	2-3
9	Visit 3, Assessor Rating	7	ASR	3-4
10	Visit 3, Resource Use Questionnaire	12	RQ1	3-4
11	Visit 3, Resource Use Questionnaire	13	RQ2	3-4
12	Visit 3, Resource Use Questionnaire	14	RQ3	3-4
13	Visit 3, Resource Use Questionnaire	15	RQ4	3-4
14	Visit 3, Resource Use Questionnaire	16	RQ5	3-4
15	Visit 3, Resource Use Questionnaire	17	RQ6	3-4
16	Visit 3, Resource Use Questionnaire	18	RQ7	3-4
17	Visit 3, Resource Use Questionnaire	19-21	RQ8	3
18	Adverse Events		ADV	
19	Withdrawal/End of Study		EOS	
20	Additional Carer Form		ACF	
21	Admission/Discharge Information		ADI	
22	Clinical Team-Delivered CPT	1	CDC	
23	Researcher-Delivered CPT	1-2	RDC	
24	Researcher-Delivered FST	1-2	RDF	
25	Pain and Fatigue	1-2	PAF	

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Appendix 2 Sample CRF Transfer Form

Robertson Centre for Biostatistics
FAST INDICATE Study
Version_1

CRF Transfer Form

Site No. _____
Transfer Form No. _____

The following completed Case Report Forms (CRFs) were dispatched to:
June Allan, Robertson Centre for Biostatistics, Level 11, Boyd Orr Building, University of Glasgow, University Avenue, Glasgow
G12 8QQ

By _____ (signature) on _____ (date)

Note:

1. PLEASE INSERT A ONE (1) FOR EACH SET OF COMPLETED CRFs SENT AND A ZERO (0) FOR CRFs NOT BEING SENT
2. FOR CRFs WHICH ARE BEING SENT BUT HAVE NOT BEEN COMPLETED, PLEASE INSERT 8 (FOR BLANK) – ALL HEADER INFORMATION MUST STILL BE COMPLETED ON THESE CRFs
3. FOR CRFs WHICH MAY BE SENT IN MULTIPLE 8 (E.G. ADVERSE EVENTS) PLEASE RECORD THE TOTAL NUMBER OF PAGES SENT

	Screening No.	Random No.	Visit 1, Screening - Pages 1-7	Visit 2, Baseline - Pages 1-17	Visit 3, Week 6 - Page 1-20	Visit 4, 6 Month Follow-up Pages 1-18	Adverse Events*	Pain and Fatigue*	Clinical Team Delivered CPT	Researcher - Delivered CPT Pages 1-2	Researcher Delivered EST Pages 1-2	Additional Cancer Form	Admission/Discharge Information	Withdrawal/End of Study
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

+/-

Please detail any problems and/or discrepancies noted at Robertson Centre:

The above CRFs were received at the Robertson Centre by:

_____ (signature) on _____ (date)

Please email completed form back to: Andrew Walker Email: Andrew.Walker@uea.ac.uk

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Appendix 3 Sample Data Amendment form

FAST INDICATE Study

Amendment Request

Randomisation Number [][][][]	Subject Initials [][][]	Date of Completion [][] / [][] / [][][] D D M M Y Y
--------------------------------------	-------------------------------	--

CRF Type

ARF No.

Visit number <input type="checkbox"/>	Adverse Events <input type="checkbox"/>	Withdrawal / End of Study <input type="checkbox"/>	Additional Care Form <input type="checkbox"/>	Admission/ Discharge Information <input type="checkbox"/>
Page No [][]	Page No [][]		Page No [][]	Page No [][]
Clinical Team-delivered CPT <input type="checkbox"/>	Researcher-delivered CPT <input type="checkbox"/>	Researcher-delivered FST <input type="checkbox"/>	Pain and Fatigue <input type="checkbox"/>	Resource Use Questionnaire <input type="checkbox"/>
Form No [][]	Form No [][]	Form No [][]		Visit No [][] Page No [][]

Question:	Change from	Change to
Reason:		

Question:	Change from	Change to
Reason:		

Date Centre Use only:

Table name	Record No.	Field ID	Change to	Review by date	Auth, by+ date

Raised by (tick one)	Study Site <input type="checkbox"/> 1	Sponsor/Monitor <input type="checkbox"/> 2	Data Centre <input type="checkbox"/> 3
Signature (Requested) & date			

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Doc Ref: Form_07.010AG

Amendment Request template V2.0

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Appendix 4 IVRS sample worksheet – V1.1

FAST Indicate Study worksheet: Randomisation

IMPORTANT:

- Please ensure that you have gathered all information required before making a call to the system.
- Steps will proceed sequentially unless otherwise noted.

IVRS NUMBER: 0141 337 4199

Step	Voice Prompt	Data values	Value entered
1	Welcome to the FAST Indicate Study IVRS		
2	Please enter your Site ID	Site ID	<input type="text"/>
	The Site ID will be checked for validity. If the Site ID does not exist an error message will result: "The Site ID you entered was not recognised. Please try again." and step 2 will be repeated.		
3	Please enter your PIN	PIN	<input type="text"/>
	Your PIN will be checked for validity. If the PIN does not exist in the system an error message will result: "The PIN you entered was not recognised" will play and you will be sent back to the start of step 3.		
4	Menu options To Randomise a patient, press 1	Menu choice	<input type="text"/>
5	Please enter the Screening Number of the patient that you want to randomise		<input type="text"/>
	<ul style="list-style-type: none"> • If an invalid response is given then the message "You entered an invalid value. Please try again." will play and you will be sent back to the start of step 5. • If a valid Screening Number is entered and it has not already been randomised then proceed to step 6. • If a valid Screening Number is entered but it has already been randomised on the system then the message "The Screening Number you entered has already been randomised. To randomise a patient with a different Screening Number press 1 or press any other button to end the call." will play. Pressing 1 in response to this message will return you to the start of step 5. Any other button will end the call. 		
6	Please specify the Time After Stroke: Press 1 for <= 30 days Press 2 for 31-60 days	Time After Stroke	<input type="text"/>
	Range: 1 (<=30 days) or 2 (31-60 days) If an invalid value (non-numeric) or out of range value is entered you will be notified and asked to repeat this step.		
7	Please specify the patient's ability to use paretic upper limb as assessed by 9HPT: Press 1 for "1 peg or less (in 50 seconds)" Press 2 for "2-8 pegs (in 50 seconds)"	9HPT	<input type="text"/>
	Range: 1 (1 peg or less) or 2 (2-8 pegs) If an invalid value (non-numeric) or out of range value is entered you will be notified and asked to repeat this step.		
8	You have now entered all values required to randomise the patient. Press 1 to continue with randomisation; Press 2 to review all the values you have just entered; or Press 3 to end the call without randomising		Enter: 1, 2 or 3 as appropriate
	Instructions: Pressing 1 will take you to step 9. If any errors occur at the randomisation step a message will play back with specific details of the error and the call will then end. Pressing 2 will play back a summary of all the values you entered above. The option will then be given to go back and re-enter the values again (Option 2) or to continue with the randomisation process (Option 1). Selecting 2 will return you to step 5, selecting 1 will proceed to step 9. Pressing 3 ends the call Range: 1, 2 or 3		

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9	<p>The patient with Screening Number <input type="text"/><input type="text"/><input type="text"/><input type="text"/><input type="text"/><input type="text"/> has been successfully randomised and has been allocated:</p> <p>Randomisation Number <input type="text"/><input type="text"/><input type="text"/><input type="text"/></p> <p>with treatment group <input type="text"/> CPT + CPT</p> <p style="padding-left: 150px;"><input type="text"/> CPT + FST</p>	
10	<p>To hear this information again press 1 or press any other button to end the call</p>	<p>Enter: 1 to hear details in 9 again; any other button to end the call</p>
Range: 1 – hear again; any other button – end call		
11	Thank you for calling goodbye	

Errors:

If the call error allowance is exceeded during a call then the caller will be played the message “The maximum number of acceptable call errors has been exceeded, the call will now end” and the call will end.

If a system error is encountered a message will play to notify you of this. If this problem persists please contact the Robertson Centre for Biostatistics for additional help.

WORKSHEET VERSION HISTORY

Version	Date	Description	Created by
Draft 1	05/09/2012	Initial version release	Robbie Wilson
1.0	12/09/2012	Updated to add IVRS number and amend incorrect step numbers	Sarah Weeden
1.1	02/10/2012	Updated to provide live IVRS number following release of live system	Sarah Weeden

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Appendix 5 Sample Data Query Form (DQF)

FAST DATA QUERY DQF No: 110

Subject: 407 Date Printed: 22/07/2010

Form: Adverse Event Visit No: N/a Page: 407
Field: Date of onset of Adverse Event Value: 15/02/2010

Form: Demographics Visit No: N/a Page: 407
Field: Date of Demographics evaluation Value: 10/03/2010 00:00:00

Record No: 10 QNo:395
Field ID: xADVONSETdat

Record No: 15 QNo:396
Field ID: xDEMOOV3

Example of the comparison of 2 data values

Problem

Question: Date of onset of Adverse Event(15/02/10) should be later or the same as Date of Demographics evaluation(10/03/10).

Please give resolution in space provided below:

Resolution

Review all values in the query and indicate clearly any data amendments that are required in the box provided. If no change is required, please give reason.

Resolved by: _____ Date: _____

Authorised by: _____ Date: _____

Signature(s) required. Single signature to resolve and authorise is acceptable.

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University of Glasgow
Doc Ref 922

Data Query Form template V1.5

Robertson Centre for Biostatistics
Glasgow Clinical Trials Unit
Doc Ref: Form_07.007a

Data Management Plan template V2.0

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Appendix 6 Sample Manual Query (MQ)

FAST

Manual Query

MQ No: 17

Date Printed: 28/07/2010

Subject: 0311 Site: 3

CRF page and question →

Table: Concomitant medication form Page: 193 FieldID: All fields
Field: All fields

Response given on form:

Query: Response is Yes to Medical History, page 6, question 4 AND Post operative visit (6 weeks) question 3 but we have not received a Concomitant medications form for this subject. Please either supply page/s or update response to no.

Suggested resolution:

Accept suggested resolution? Yes ☐ (If not, please give resolution in space provided below)

Review question. If a suggested resolution has been given and that is acceptable, tick the Yes box. If response is required, please indicate clearly what action is required.

Resolved by: _____ Date: _____
Authorised by: _____ Date: _____
Version: 1.0 Robertson Centre for Biostatistics

Signature(s) required.
Single signature to resolve and authorise is acceptable.

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME
HS&DR
HTA
PGfAR
PHR**

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